(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/057450 A2

(51) International Patent Classification[7]: C12N 15/12, C07K 14/47, 16/18, C12N 15/11, G01N 33/68, 33/574, C12Q 1/68, A61K 31/713, 39/395, 38/17, 31/7088, A61P 9/10, 35/00, 3/10, A01K 67/027

(21) International Application Number: PCT/US01/48922

(22) International Filing Date:
29 November 2001 (29.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/253,834	29 November 2000 (29.11.2000)	US
60/250,926	30 November 2000 (30.11.2000)	US
60/264,180	25 January 2001 (25.01.2001)	US
60/313,656	20 August 2001 (20.08.2001)	US
60/327,456	5 October 2001 (05.10.2001)	US
Not furnished	28 November 2001 (28.11.2001)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US Not furnished (CIP)
Filed on 28 November 2001 (28.11.2001)

(71) Applicant *(for all designated States except US)*: **CURAGEN CORPORATION** [US/US]; 555 Long Wharf Drive, 11th floor, New Haven, CT 06511 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **EDINGER, Shlomit** [US/US]; 766 Edgewood Avenue, New Haven, CT 06515 (US). **MACDOUGALL, John, R.** [CA/US]; 117 Russell Street, Hamden, CT 06515 (US). **MILLET, Isabelle** [FR/US]; 74 Carrington Avenue, Milford, CT 06460 (US). **ELLERMAN, Karen** [US/US]; 87 Montoya Drive, Branford, CT 06405 (US). **STONE, David, J.** [US/US]; 223 Whitethorn Drive, Guilford, CT 06437 (US). **GERLACH, Valerie** [US/US]; 18 Rock Pasture Road, Branford, CT 06405 (US). **GROSSE, William, M.** [US/US]; 15 Rice Terrace Road, Apartment C, Branford, CT 06405 (US). **ALSOBROOK, John, P., II** [US/US]; 60 Lake Drive, Madison, CT 06443 (US). **LEPLEY, Denise, M.** [US/US]; 51 Church Street, Branford, CT 06405 (US). **RIEGER, Daniel** [US/US]; 555 Long Wharf Drive, 11th Floor, New Haven, CT 06405 (US). **BURGESS, Catherine, E.** [US/US]; 90 Carriage Hill Drive, Weathersfield, CT 06109 (US). **CASMAN, Stacie, J.** [US/US]; 17 Peck Street, North Haven, CT 06473 (US). **SPYTEK, Kimberly, A.** [US/US]; 28 Court Street #1, New Haven, CT 06511 (US). **BOLDOG, Ferenc, L.** [HU/US]; 1687 Hartford Turnpike, North Haven, CT 06473 (US). **LI, Li** [CN/US]; 56 Jerimoth Drive, Branford, CT 06405 (US). **PADIGARU, Muralindhara** [IN/US]; 71 Hampton Park, Branford, CT 06405 (US). **MISHRA, Vishnu** [IN/US]; 3832 SW 93rd Terrace, Gainesville, FL 32608 (US). **PATTURAJAN, Meera** [IN/US]; 45 Harrison Avenue, Apartment 1C, Branford, CT 06405 (US). **SHENOY, Suresh** [IN/US]; 15 Millwood Drive, Branford, CT 06405 (US). **RASTELLI, Luca** [IT/US]; 52 Pepperbush Lane, Guilford, CT 06437 (US). **TCHERNEV, Velizar, T.** [BG/US]; 45 Jefferson Road, #3-12, Branford, CT 06405 (US). **VERNET, Corine, A., M.** [FR/US]; 1739 Foxon Road, Apartment L6, North Branford, CT 06471 (US). **ZERHUSEN, Bryan, D.** [US/US]; 337 Monticello Drive, Branford, CT 06405 (US). **MALYANKAR, Uriel, M.** [IN/US]; 229 Branford Road, # 330, Branford, CT 06405 (US). **GUO, Xiyojia** [CN/US]; 713 Robert Frost Drive, Branford, CT 06405 (US). **MILLER, Charles, E.** [US/US]; 98 Saddle Hill Drive, Guilford, CT 06437 (US). **GANGOLLI, Esha, A.** [IN/US]; 31 Strawberry Hill Road, Madison, CT 06443 (US).

(74) Agent: **ELRIFI, Ivor, R.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: PROTEINS AND NUCLEIC ACIDS ENCODING SAME

(57) Abstract: Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

WO 02/057450 A2

Published:
— *without international search report and to be republished upon receipt of that report*
— *entirely in electronic form (except for this front page) and available upon request from the International Bureau*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PROTEINS AND NUCLEIC ACIDS ENCODING SAME

FIELD OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded thereby.

BACKGROUND OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded therefrom. More specifically, the invention relates to nucleic acids encoding cytoplasmic, nuclear, membrane bound, and secreted polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

SUMMARY OF THE INVENTION

The invention is based in part upon the discovery of nucleic acid sequences encoding novel polypeptides. The novel nucleic acids and polypeptides are referred to herein as NOVX, or NOV1, NOV2, NOV3, NOV4, NOV5, NOV6, NOV7, NOV8, NOV9, NOV10, NOV11, and NOV12 nucleic acids and polypeptides. These nucleic acids and polypeptides, as well as derivatives, homologs, analogs and fragments thereof, will hereinafter be collectively designated as "NOVX" nucleic acid or polypeptide sequences.

In one aspect, the invention provides an isolated NOVX nucleic acid molecule encoding a NOVX polypeptide that includes a nucleic acid sequence that has identity to the nucleic acids disclosed in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31. In some embodiments, the NOVX nucleic acid molecule will hybridize under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule that includes a protein-coding sequence of a NOVX nucleic acid sequence. The invention also includes an isolated nucleic acid that encodes a NOVX polypeptide, or a fragment, homolog, analog or derivative thereof. For example, the nucleic acid can encode a polypeptide at least 80% identical to a polypeptide comprising the amino acid sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32. The nucleic acid can be, for example, a genomic DNA fragment or a cDNA molecule that includes the nucleic acid sequence of any of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31.

Also included in the invention is an oligonucleotide, *e.g.*, an oligonucleotide which includes at least 6 contiguous nucleotides of a NOVX nucleic acid (*e.g.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31) or a complement of said oligonucleotide.

Also included in the invention are substantially purified NOVX polypeptides (SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32). In certain embodiments, the NOVX polypeptides include an amino acid sequence that is substantially identical to the amino acid sequence of a human NOVX polypeptide.

The invention also features antibodies that immunoselectively bind to NOVX polypeptides, or fragments, homologs, analogs or derivatives thereof.

In another aspect, the invention includes pharmaceutical compositions that include therapeutically- or prophylactically-effective amounts of a therapeutic and a pharmaceutically-acceptable carrier. The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or an antibody specific for a NOVX polypeptide. In a further aspect, the invention includes, in one or more containers, a therapeutically- or prophylactically-effective amount of this pharmaceutical composition.

In a further aspect, the invention includes a method of producing a polypeptide by culturing a cell that includes a NOVX nucleic acid, under conditions allowing for expression of the NOVX polypeptide encoded by the DNA. If desired, the NOVX polypeptide can then be recovered.

In another aspect, the invention includes a method of detecting the presence of a NOVX polypeptide in a sample. In the method, a sample is contacted with a compound that selectively binds to the polypeptide under conditions allowing for formation of a complex between the polypeptide and the compound. The complex is detected, if present, thereby identifying the NOVX polypeptide within the sample.

The invention also includes methods to identify specific cell or tissue types based on their expression of a NOVX.

Also included in the invention is a method of detecting the presence of a NOVX nucleic acid molecule in a sample by contacting the sample with a NOVX nucleic acid probe or primer, and detecting whether the nucleic acid probe or primer bound to a NOVX nucleic acid molecule in the sample.

In a further aspect, the invention provides a method for modulating the activity of a NOVX polypeptide by contacting a cell sample that includes the NOVX polypeptide with a compound that binds to the NOVX polypeptide in an amount sufficient to modulate the activity of said polypeptide. The compound can be, *e.g.*, a small molecule, such as a nucleic acid, peptide, polypeptide, peptidomimetic, carbohydrate, lipid or other organic (carbon containing) or inorganic molecule, as further described herein.

Also within the scope of the invention is the use of a therapeutic in the manufacture of a medicament for treating or preventing disorders or syndromes including, *e.g.*, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, hypercoagulation, hemophilia, idiopathic thrombocytopenic purpura, heart failure, secondary pathologies caused by heart failure and hypertension, hypotension, angina pectoris, myocardial infarction, tuberous sclerosis, scleroderma, transplantation, autoimmune disease, lupus erythematosus, viral/bacterial/parasitic infections, multiple sclerosis, autoimmume disease, allergies, immunodeficiencies, graft versus host disease, asthma, emphysema, ARDS, inflammation and modulation of the immune response, viral pathogenesis, aging-related disorders, Th1 inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, AIDS, wound repair, obesity, diabetes, endocrine disorders, anorexia, bulimia, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic, renal tubular acidosis, IgA nephropathy, nephrological disesases, hypercalceimia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, trauma, regeneration (in vitro and in vivo), Hirschsprung's disease , Crohn's Disease, appendicitis, endometriosis, laryngitis, psoriasis, actinic keratosis, acne, hair growth/loss, allopecia, pigmentation disorders, myasthenia gravis, alpha-mannosidosis, beta-mannosidosis, other storage disorders, peroxisomal disorders such as zellweger syndrome, infantile refsum disease, rhizomelic chondrodysplasia (chondrodysplasia punctata, rhizomelic), and hyperpipecolic acidemia, osteoporosis, muscle disorders, urinary retention, Albright Hereditary Ostoeodystrophy, ulcers, Alzheimer's disease, stroke, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, behavioral disorders, addiction, anxiety, pain, neuroprotection, Stroke, Aphakia, neurodegenerative disorders, neurologic disorders, developmental defects, conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors, encephalomyelitis, anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, Gilles de la Tourette syndrome, leukodystrophies, cancers, breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, kidney cancer, colon cancer, prostate cancer, neuroblastoma, and cervical cancer, Neoplasm; adenocarcinoma, lymphoma; uterus cancer, benign prostatic hypertrophy, fertility, control of growth and development/differentiation related functions such as but not limited

maturation, lactation and puberty, reproductive malfunction, and/or other pathologies and disorders of the like.

The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or a NOVX-specific antibody, or biologically-active derivatives or fragments thereof.

For example, the compositions of the present invention will have efficacy for treatment of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The polypeptides can be used as immunogens to produce antibodies specific for the invention, and as vaccines. They can also be used to screen for potential agonist and antagonist compounds. For example, a cDNA encoding NOVX may be useful in gene therapy, and NOVX may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

The invention further includes a method for screening for a modulator of disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The method includes contacting a test compound with a NOVX polypeptide and determining if the test compound binds to said NOVX polypeptide. Binding of the test compound to the NOVX polypeptide indicates the test compound is a modulator of activity, or of latency or predisposition to the aforementioned disorders or syndromes.

Also within the scope of the invention is a method for screening for a modulator of activity, or of latency or predisposition to disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like by administering a test compound to a test animal at increased risk for the aforementioned disorders or syndromes. The test animal expresses a recombinant polypeptide encoded by a NOVX nucleic acid. Expression or activity of NOVX polypeptide is then measured in the test animal, as is expression or activity of the protein in a control animal which recombinantly-expresses NOVX polypeptide and is not at increased risk for the disorder or syndrome. Next, the expression of NOVX polypeptide in both the test animal and the control animal is compared. A change in the activity of NOVX polypeptide in the test animal relative to the control animal indicates the test compound is a modulator of latency of the disorder or syndrome.

In yet another aspect, the invention includes a method for determining the presence of or predisposition to a disease associated with altered levels of a NOVX polypeptide, a NOVX nucleic acid, or both, in a subject (*e.g.*, a human subject). The method includes measuring the

amount of the NOVX polypeptide in a test sample from the subject and comparing the amount of the polypeptide in the test sample to the amount of the NOVX polypeptide present in a control sample. An alteration in the level of the NOVX polypeptide in the test sample as compared to the control sample indicates the presence of or predisposition to a disease in the subject. Preferably, the predisposition includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. Also, the expression levels of the new polypeptides of the invention can be used in a method to screen for various cancers as well as to determine the stage of cancers.

In a further aspect, the invention includes a method of treating or preventing a pathological condition associated with a disorder in a mammal by administering to the subject a NOVX polypeptide, a NOVX nucleic acid, or a NOVX-specific antibody to a subject (*e.g.*, a human subject), in an amount sufficient to alleviate or prevent the pathological condition. In preferred embodiments, the disorder, includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

In yet another aspect, the invention can be used in a method to identity the cellular receptors and downstream effectors of the invention by any one of a number of techniques commonly employed in the art. These include but are not limited to the two-hybrid system, affinity purification, co-precipitation with antibodies or other specific-interacting molecules.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel nucleotides and polypeptides encoded thereby. Included in the invention are the novel nucleic acid sequences and their encoded polypeptides. The sequences are collectively referred to herein as "NOVX nucleic acids" or "NOVX

polynucleotides" and the corresponding encoded polypeptides are referred to as "NOVX polypeptides" or "NOVX proteins." Unless indicated otherwise, "NOVX" is meant to refer to any of the novel sequences disclosed herein. Table A provides a summary of the NOVX nucleic acids and their encoded polypeptides.

TABLE A. Sequences and Corresponding SEQ ID Numbers

NOVX Assignment	Internal Identification	SEQ ID NO (nucleic acid)	SEQ ID NO (polypeptide)	Homology
1a	GMba58o1_A_da1	1	2	Transmembrane receptor UNC5H2-like
1b	Gmba58o1_A	3	4	Transmembrane receptor UNC5H2-like
2a	SC126422078_A	5	6	Tyrosine Phosphatase Precursor-like
2b	CG50718-02	7	8	Glomerular Mesangial Cell Receptor Protein Tyrosine Phosphatase Precursor like
2c	CG50718-05	9	10	Glomerular Mesangial Cell Receptor Protein Tyrosine Phosphatase Precursor like
3	134899552_EXT	11	12	Human homolog of the Drosophila pecanex-like
4	SC140515441_A	13	14	Aurora-related kinase 1-like
5	SC44326718_A	15	16	26S protease regulatory subunit 4-like
6	GMAC073364_Ada1	17	18	Mitsugumin29-like
7	106973211_EXT	19	20	Wnt-15-like
8	88091010-EXT	21	22	Wnt-14-like
9	AC069250_28_da1	23	24	Beta-adrenergic receptor kinase-like
10	AC058790_da25	25	26	Alpha-mannosidase-like
11a	GM57107065_da1	27	28	C1q-related factor-like
11b	CG54503-02	29	30	C1q-related factor-like
12	SC132340676_A	31	32	Plexin 1-like

NOVX nucleic acids and their encoded polypeptides are useful in a variety of applications and contexts. The various NOVX nucleic acids and polypeptides according to the invention are useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. Additionally, NOVX nucleic acids and polypeptides can also be used to identify proteins that are members of the family to which the NOVX polypeptides belong.

NOV1 is homologous to the transmembrane receptor UNC5H2-like family of proteins. Thus, NOV1 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus,

pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, cancers, and/or other pathologies and disorders. Also since this gene is expressed at a measurably higher level in several cancer cell lines (including breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer and pancreatic cancer), it may be useful in diagnosis and treatment of these cancers.

NOV2 is homologous to the protein tyrosine phosphatase precursor-like family of proteins. Thus NOV2 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; cancer, kidney cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, nephrological disesases including diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, Lesch-Nyhan syndrome, Hirschsprung's disease , Crohn's Disease, appendicitis, and/or other pathologies and disorders.

NOV3 is homologous to the Human homolog of the Drosophila pecanex family of proteins. Thus NOV3 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; cancer,trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, multiple sclerosis, scleroderma, obesity, endometriosis, fertility, hypercoagulation, autoimmume disease, allergies, immunodeficiencies, transplantation, hemophilia, idiopathic thrombocytopenic purpura, graft versus host disease, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, systemic lupus erythematosus, asthma, emphysema, ARDS, laryngitis, psoriasis, actinic keratosis, acne, hair growth/loss,

allopecia, pigmentation disorders, endocrine disorders, diabetes, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, Lesch-Nyhan syndrome, and a variety of kidney diseases and/or other pathologies and disorders.

NOV4 is homologous to a family of Aurora-related kinase 1-like proteins. Thus, the NOV4 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer, Cardiomyopathy, Atherosclerosis, Hypertension, Congenital heart defects, Aortic stenosis, Atrial septal defect (ASD), Atrioventricular (A-V) canal defect, Ductus arteriosus, Pulmonary stenosis, Subaortic stenosis, Ventricular septal defect (VSD), valve diseases, Tuberous sclerosis, Scleroderma, Obesity, Transplantation, Diabetes, Von Hippel-Lindau (VHL) syndrome, Pancreatitis, Alzheimer's disease, Stroke, hypercalceimia, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Lesch-Nyhan syndrome, Multiple sclerosis, Ataxia-telangiectasia, Leukodystrophies, Behavioral disorders, Addiction, Anxiety, Pain, and Neuroprotection, and/or other pathologies.

NOV5 is homologous to the 26S protease regulatory subunit 4-like family of proteins. Thus, NOV5 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: cataract and Aphakia, Alzheimer's disease, neurodegenerative disorders, inflammation and modulation of the immune response, viral pathogenesis, aging-related disorders, neurologic disorders, cancer, and/or other pathologies.

NOV6 is homologous to the MITSUGUMIN29-like family of proteins. Thus, NOV6 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy , congenital adrenal hyperplasia, and other diseases, disorders and conditions of the like. Also since the invention is highly

expressed in one of the lung cancer cell lines (Lung cancer NCI-H522), it may be useful in diagnosis and treatment of this cancer.

NOV7 is homologous to the Wnt-15-like family of proteins. Thus NOV7 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in Von Hippel-Lindau (VHL) syndrome , Alzheimer's disease, stroke, tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies/disorders.

NOV8 is homologous to members of the Wnt-14-like family of proteins. Thus, the NOV8 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; Von Hippel-Lindau (VHL) syndrome , Alzheimer's disease, stroke, tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies/disorders.

NOV9 is homologous to the beta adrenergic receptor kinase-like family of proteins. Thus, NOV9 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: heart failure, hypertension, secondary pathologies caused by heart failure and hypertension, and other diseases, disorders and conditions of the like. Additionally, the compositions of the present invention may have efficacy for treatment of patients suffering from conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors.

NOV10 is homologous to the alpha-mannosidase-like family of proteins. Thus, NOV10 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: alpha-mannosidosis, beta-mannosidosis, other storage disorders, peroxisomal disorders such as zellweger syndrome, infantile refsum disease, rhizomelic chondrodysplasia (chondrodysplasia punctata, rhizomelic), and hyperpipecolic acidemia and other diseases, disorders and conditions of the like, and/or other pathologies/disorders.

NOV11 is homologous to the C1q-related factor-like family of proteins. Thus, NOV11 nucleic acids and polypeptides, antibodies and related compounds according to the invention

will be useful in therapeutic and diagnostic applications implicated in, for example: Th1 inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases and psoriasis, lupus erythematosus and glomerulonephritis, control of growh and development/differentiation related functions such as but not limited maturation, lactation and puberty, osteoporosis, obesity, aging and reproductive malfunction and hence could be used in treatment and/or diagnosis of these disorders.

NOV12 is homologous to the Plexin-1 like family of proteins. Thus, NOV12 nucleic acids and polypeptides, antibodies, and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: AIDS, cancer therapy, treatment of Neurologic diseases, Brain and/or autoimmune disorders like encephalomyelitis, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, endocrine diseases, muscle disorders, inflammation and wound repair, bacterial, fungal, protozoal and viral infections (particularly infections caused by HIV-1 or HIV-2), pain, cancer (including but not limited to Neoplasm; adenocarcinoma; lymphoma; prostate cancer; uterus cancer), anorexia, bulimia, asthma, Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, Crohn's disease; multiple sclerosis; and Treatment of Albright Hereditary Ostoeodystrophy, angina pectoris, myocardial infarction, ulcers, asthma, allergies, benign prostatic hypertrophy, and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette syndrome, and/or other pathologies/disorders.

The NOVX nucleic acids and polypeptides can also be used to screen for molecules, which inhibit or enhance NOVX activity or function. Specifically, the nucleic acids and polypeptides according to the invention may be used as targets for the identification of small molecules that modulate or inhibit, *e.g.*, neurogenesis, cell differentiation, cell proliferation, hematopoiesis, wound healing and angiogenesis.

Additional utilities for the NOVX nucleic acids and polypeptides according to the invention are disclosed herein.

NOV1

NOV1 includes three novel transmembrane receptor UNC5H2-like proteins disclosed below. The disclosed sequences have been named NOV1a and NOV1b.

NOV1a

A disclosed NOV1a nucleic acid of 2860 nucleotides (also referred to as GMba58o1_A_da1) encoding a transmembrane receptor UNC5H2-like protein is shown in Table 1A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 59-61 and ending with a TGA codon at nucleotides 2858-2860. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 1A. The start and stop codons are in bold letters.

Table 1A. NOV1a nucleotide sequence (SEQ ID NO:1).

AGACTGGGGCCAGGGAGACAGCCCTGGGGGAGAGGCGCCCGAACCAGGCCGCGGGAGC**ATG**GGGGCCCGGAG
CGGAGCTCGGGGCGCGCTGCTGCTGGCACTGCTGCTCTGCTGGGACCCGAGGCTGAGCCAAGCAGGCACTGA
TTCTGGCAGCGAGGTGCTCCCTGACTCCTTCCCGTCAGCGCCAGCAGAGCCGCTGCCCTACTTCCTGCAGGA
GCCACAGGACGCCTACATTGTGAAGAACAAGCCTGTGGAGCTCCGCTGCCGCGCCTTCCCCGCCACACAGAT
CTACTTCAAGTGCAACGGCGAGTGGGTCAGCCAGAACGACCACGTCACACAGGAAGGCCTGGATGAGGCCAC
CGGTCTGCGGGTGCGCGAGGTGCAGATCGAGGTGTCGCGGCAGCAGGTGGAGGAGCTCTTTGGGCTGGAGGA
TTACTGGTGCCAGTGCGTGGCCTGGAGCTCCGCGGGCACCACCAAGAGTCGCCGAGCCTACGTCCGCATCGC
CTACCTGCGCAAGAACTTCGATCAGGAGCCTCTGGGCAAGGAGGTGCCCCTGGACCATGAGGTTCTCCTGCA
GTGCCGCCCGCCGGAGGGGGTGCCTGTGGCCGAGGTGGAATGGCTCAAGAATGAGGATGTCATCGACCCCAC
CCAGGACACCAACTTCCTGCTCACCATCGACCACAACCTCATCATCCGCCAGGCCCGCCTGTCGGACACTGC
CAACTATACCTGCGTGGCCAAGAACATCGTGGCCAAACGCCGGAGCACCACTGCCACCGTCATCGTCTACGT
GAATGGCGGCTGGTCCAGCTGGGCAGAGTGGTCACCCTGCTCCAACCGCTGTGGCCGAGGCTGGCAGAAGCG
CACCCGGACCTGCACCAACCCCGCTCCACTCAACGGAGGGGCCTTCTGCGAGGGCCAGGCATTCCAGAAGAC
CGCCTGCACCACCATCTGCCCAGTCGATGGGGCGTGGACGGAGTGGAGCAAGTGGTCAGCCTGCAGCACTGA
GTGTGCCCACTGGCGTAGCCGCGAGTGCATGGCGCCCCCACCCCAGAACGGAGGCCGTGACTGCAGCGGGAC
GCTGCTCGACTCTAAGAACTGCACAGATGGGCTGTGCATGCAACTGGAGGCCTCAGGGGATGCGGCGCTGTA
TGCGGGGCTCGTGGTGGCCATCTTCGTGGTCGTGGCAATCCTCATGGCGGTGGGGGTGGTGGTGTACCGCCG
CAACTGCCGTGACTTCGACACAGACATCACTGACTCATCTGCTGCCCTGACTGGTGGTTTCCACCCCGTCAA
CTTTAAGACGGCAAGGCCCAGTAACCCGCAGCTCCTACACCCCTCTGTGCCTCCTGACCTGACAGCCAGCGC
CGGCATCTACCGCGGACCCGTGTATGCCCTGCAGGACTCCACCGACAAAATCCCCATGACCAACTCTCCTCT
GCTGGACCCCTTACCCAGCCTTAAGGTCAAGGTCTACAGCTCCAGCACCACGGGCTCTGGGCCAGGCCTGGC
AGATGGGGCTGACCTGCTGGGGGTCTTGCCGCCTGGCACATACCCTAGCGATTTCGCCCGGGACACCCACTT
CCTGCACCTGCGCAGCGCCAGCCTCGGTTCCCAGCAGCTCTTGGGCCTGCCCCGAGACCCAGGGAGCAGCGT
CAGCGGCACCTTTGGCTGCCTGGGTGGGAGGCTCAGCATCCCCGGCACAGGGGTCAGCTTGCTGGTGCCCAA
TGGAGCCATTCCCCAGGGCAAGTTCTACGAGATGTATCTACTCATCAACAAGGCAGAAAGTACCCTGCCGCT
TTCAGAAGGGACCCAGACAGTATTGAGCCCCTCGGTGACCTGTGGACCCACAGGCCTCCTGCTGTGCCGCCC
CGTCATCCTCACCATGCCCCACTGTGCCGAAGTCAGTGCCCGTGACTGGATCTTTCAGCTCAAGACCCAGGC
CCACCAGGGCCACTGGGAGGAGGTGGTGACCCTGGATGAGGAGACCCTGAACACACCCTGCTACTGCCAGCT
GGAGCCCAGGGCCTGTCACATCCTGCTGGACCAGCTGGGCACCTACGTGTTCACGGGCGAGTCCTATTCCCG
CTCAGCAGTCAAGCGGCTCCAGCTGGCCGTCTTCGCCCCCGCCCTCTGCACCTCCCTGGAGTACAGCCTCCG
GGTCTACTGCCTGGAGGACACGCCTGTAGCACTGAAGGAGGTGCTGGAGCTGGAGCGGACTCTGGGCGGATA
CTTGGTGGAGGAGCCGAAACCGCTAATGTTCAAGGACAGTTACCACAACCTGCGCCTCTCCCTCCATGACCT
CCCCCATGCCCATTGGAGGAGCAAGCTGCTGGCCAAATACCAGGAGATCCCCTTCTATCACATTTGGAGTGG
CAGCCAGAAGGCCCTCCACTGCACTTTCACCCTGGAGAGGCACAGCTTGGCCTCCACAGAGCTCACCTGCAA
GATCTGCGTGCGGCAAGTGGAAGGGGAGGGCCAGATATTCCAGCTGCATACCACTCTGGCAGAGACACCTGC
TGGCTCCCTGGACACTCTCTGCTCTGCCCCTGGCAGCACTGTCACCACCCAGCTGGGACCTTATGCCTTCAA
GATCCCACTGTCCATCCGCCAGAAGATATGCAACAGCCTAGATGCCCCCAACTCACGGGGCAATGACTGGCG
GATGTTAGCACAGAAGCTCTCTATGGACCGGTACCTGAATTACTTTGCCACCAAAGCGAGCCCCACGGGTGT
GATCCTGGACCTCTGGGAAGCTCTGCAGCAGGACGATGGGGACCTCAACAGCCTGGCGAGTGCCTTGGAGGA
GATGGGCAAGAGTGAGATGCTGGTGGCTGTGGCCACCGACGGGGACTGC**TGA**

In a search of public sequence databases, the NOV1a nucleic acid sequence, located on chromsome 10 has 1604 of 1895 bases (84%) identical to a transmembrane receptor UNC5H2 mRNA from *Rattus Norvegicus*, (GENBANK-ID: RNU87306). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

In all BLAST alignments herein, the "E-value" or "Expect" value is a numeric indication of the probability that the aligned sequences could have achieved their similarity to the BLAST query sequence by chance alone, within the database that was searched. For example, the probability that the subject ("Sbjct") retrieved from the NOV1a BLAST analysis, *e.g.*, transmembrane receptor UNC5H2 mRNA from *Rattus Norvegicus,* matched the Query NOV1a sequence purely by chance is 0.0. The Expect value (E) is a parameter that describes the number of hits one can "expect" to see just by chance when searching a database of a particular size. It decreases exponentially with the Score (S) that is assigned to a match between two sequences. Essentially, the E value describes the random background noise that exists for matches between sequences.

The Expect value is used as a convenient way to create a significance threshold for reporting results. The default value used for blasting is typically set to 0.0001. In BLAST 2.0, the Expect value is also used instead of the P value (probability) to report the significance of matches. For example, an E value of one assigned to a hit can be interpreted as meaning that in a database of the current size one might expect to see one match with a similar score simply by chance. An E value of zero means that one would not expect to see any matches with a similar score simply by chance. See, e.g., http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/. Occasionally, a string of X's or N's will result from a BLAST search. This is a result of automatic filtering of the query for low-complexity sequence that is performed to prevent artifactual hits. The filter substitutes any low-complexity sequence that it finds with the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNN") or the letter "X" in protein sequences (e.g., "XXXXXXXXX"). Low-complexity regions can result in high scores that reflect compositional bias rather than significant position-by-position alignment. (Wootton and Federhen, *Methods Enzymol* 266:554-571, 1996).

The disclosed NOV1a polypeptide (SEQ ID NO:2) encoded by SEQ ID NO:1 has 933 amino acid residues and is presented in Table 1B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV1a has a signal peptide at the first 26 amino acids and is likely to be localized at the plasma membrane with a certainty of 0.5140. In other embodiments, NOV1a is likely to be localized to the microbody (peroxisome) with a certainty of 0.1064, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, or to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV1a is between positions 26 and 27: SQA-GT

Table 1B. Encoded NOV1a protein sequence (SEQ ID NO:2).

```
MGARSGARGALLLALLLCWDPRLSQAGTDSGSEVLPDSFPSAPAEPLPYFLQEPQDAYIVKNKPVELRCRAF
PATQIYFKCNGEWVSQNDHVTQEGLDEATGLRVREVQIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRA
YVRIAYLRKNFDQEPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLKNEDVIDPTQDTNFLLTIDHNLIIRQAR
LSDTANYTCVAKNIVAKRRSTTATVIVYVNGGWSSWAEWSPCSNRCGRGWQKRTRTCTNPAPLNGGAFCEGQ
AFQKTACTTICPVDGAWTEWSKWSACSTECAHWRSRECMAPPPQNGGRDCSGTLLDSKNCTDGLCMQLEASG
DAALYAGLVVAIFVVVAILMAVGVVVYRRNCRDFDTDITDSSAALTGGFHPVNFKTARPSNPQLLHPSVPPD
LTASAGIYRGPVYALQDSTDKIPMTNSPLLDPLPSLKVKVYSSSTTGSGPGLADGADLLGVLPPGTYPSDFA
RDTHFLHLRSASLGSQQLLGLPRDPGSSVSGTFGCLGGRLSIPGTGVSLLVPNGAIPQGKFYEMYLLINKAE
STLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMPHCAEVSARDWIFQLKTQAHQGHWEEVVTLDEETLNTP
CYCQLEPRACHILLDQLGTYVFTGESYSRSAVKRLQLAVFAPALCTSLEYSLRVYCLEDTPVALKEVLELER
TLGGYLVEEPKPLMFKDSYHNLRLSLHDLPHAHWRSKLLAKYQEIPFYHIWSGSQKALHCTFTLERHSLAST
ELTCKICVRQVEGEGQIFQLHTTLAETPAGSLDTLCSAPGSTVTTQLGPYAFKIPLSIRQKICNSLDAPNSR
GNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQQDDGDLNSLASALEEMGKSEMLVAVATDGDC
```

A search of sequence databases reveals that the NOV1a amino acid sequence has 862 of 945 amino acid residues (91%) identical to, and 897 of 945 amino acid residues (94%) similar to, the 945 amino acid residue 6330415E02RIK protein from *Mus musculus* (Q9D398) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV1a is at least expressed in endothelial cells, heart, kidney, adipose, brain (hippocampus), brain (thalamus), cerebral cortex, and the following cancer cell lines: breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer and pancreatic cancer at a measurably higher level than the following tissues: adrenal gland, bladder, bone barrow, brain (amygdala), brain (cerebellum), brain (whole), breast, colorectal, liver, lung, lymph nod, mammary gland, ovary, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, and uterus.

NOV1b

A disclosed NOV1b nucleic acid of 2860 nucleotides (also referred to as CG50126-02) encoding a novel beta-adrenergic receptor kinase-like protein is shown in Table 1C. An open reading frame was identified beginning with an ATG codon at nucleotides 59-61, and ending with a TGA codon at nucleotides 2858-2860. Putative untranslated regions, if any, are located upstream from the initiation codon and downstream from the termination codon.

Table 1C. NOV1b nucleotide sequence (SEQ ID NO:3).

AGACTGGGGCCAGGGAGACAGCCCTGGGGGAGAGGCGCCCGAACCAGGCCGCGGGAACATGGGGGCCCGGAGCGGAGCTC
GGGGCGCGCTGCTGCTGGCACTGCTGCTCTGCTGGGACCCGAGGCTGAGCCAAGCAGGCACTGATTCTGGCAGCGAGGTG
CTCCCTGACTCCTTCCCGTCAGCGCCAGCAGAGCCGCTGCCCTACTTCCTGCAGGAGCCACAGGACGCCTACATTGTGAA
GAACAAGCCTGTGGAGCTTCGCTGCCGCGGCCTTCCCCGCCACACAGATCTACTTCAAGTGCAACGGCGAGTGGGTCAGCC
AGAACGACCACGTCACACAGGAAGGCCTGGATGAGGCCACCGGCCTGCGGGTGCGCGAGGTGCAGATCGAGGTGTCGCGG
CAGCAGGTGGAGGAGCTCTTTGGGCTGGAGGATTACTGGTGCCAGTGCGTGGCCTGGAGCTCCGCAGGCACCACCAAGAG
TCGCCGAGCCTACGTCCGCATCGCCTACCTGCGCAAGAACTTCGATCAGGAGCCTCTGGGCAAGGAGGTGCCCCTGGACC
ATGAGGTTCTCCTGCAGTGCCGCCCGCCGGAGGGGGTGCCTGTGGCCGAGGTGGAATGGCTCAAGAATGAGGATGTCATC
GACCCCACCCAGGACACCAACTTCCTGCTCACCATCGACCACAACCTCATCATCCGCCAGGCCCGCCTGTCGGACACTGC
CAACTATACCTGCGTGGCCAAGAACATCGTGGCCAAACGCCGGAGCACCACTGCCACCGTCATCGTCTACGTGAATGGCG
GCTGGTCCAGCTGGGCAGAGTGGTCACCCTGCTCCAACCGCTGTGGCCGAGGCTGGCAGAAGCGCACCCGGACCTGCACC
AACCCCGCTCCACTCAACGGAGGGGCCTTCTGCGAGGGCCAGGCATTCCAGAAGACCGCCTGCACCACCATCTGCCCAGT
CGATGGGGCGTGGACGGAGTGGAGCAAGTGGTCAGCCTGCAGCACTGAGTGTGCCCACTGGCGTAGCCGCGAGTGCATGG
CGCCCCCACCCCAGAACGGAGGCCGTGACTGCAGCGGGACGCTGCTCGACTCTAAGAACTGCACAGATGGGCTGTGCATG
CAACTGGAGGCCTCAGGGGATGCGGCGCTGTATGCGGGGCTCGTGGTGGCCATCTTCGTGGTCGTGGCAATCCTCATGGC
GGTGGGGGTGGTGGTGTACCGCCGCAACTGCCGTGACTTCGACACAGACATCACTGACTCATCTGCTGCCCTGACTGGTG
GTTTCCACCCCGTCAACTTTAAGACGGCAAGGCCCAGTAACCCGCAGCTCCTACACCCCTCTGTGCCTCCTGACCTGACA
GCCAGCGCCGGCATCTACCGCGGACCCGTGTATGCCCTGCAGGACTCCACCGACAAAATCCCCATGACCAACTCTCCTCT
GCTGGACCCCTTACCCAGCCTTAAGGTCAAGGTCTACAGCTCCAGCACCACGGGCTCTGGGCCAGGCCTGGCAGATGGGG
CTGACCTGCTGGGGGTCTTGCCGCCTGGCACATACCCTAGCGATTTCGCCCGGGACACCCACTTCCTGCACCTGCGCAGC
GCCAGCCTCGGTTCCCAGCAGCTCTTGGGCCTGCCCCGAGACCCAGGGAGCAGCGTCAGCGGCACCTTTGGCTGCCTGGG
TGGGAGGCTCAGCATCCCCGGCACAGGGGTCAGCTTGCTGGTGCCCAATGGAGCCATTCCCCAGGGCAAGTTCTACGAGA
TGTATCTACTCATCAACAAGGCAGAAAGTACCCTGCCGCTTTCAGAAGGGACCCAGACAGTATTGAGCCCCTCGGTGACC
TGTGGACCCACAGGCCTCCTGCTGTGCCGCCCCGTCATCCTCACCATGCCCCACTGTGCCGAAGTCAGTGCCCGTGACTG
GATCTTTCAGCTCAAGACCCAGGCCCACCAGGGCCACTGGGAGGAGGTGGTGACCCTGGATGAGGAGACCCTGAACACAC
CCTGCTACTGCCAGCTGGAGCCCAGGGCCTGTCACATCCTGCTGGACCAGCTGGGCACCTACGTGTTCACGGGCGAGTCC
TATTCCCGCTCAGCAGTCAAGCGGCTCCAGCTGGCCGTCTTCGCCCCCGCCCTCTGCACCTCCCTGGAGTACAGCCTCCG
GGTCTACTGCCTGGAGGACACGCCTGTAGCACTGAAGGAGGTGCTGGAGCTGGAGCGGACTCTGGGCGGATACTTGGTGG
AGGAGCCGAAACCGCTAATGTTCAAGGACAGTTACCACAACCTGCGCCTCTCCCTCCATGACCTCCCCCATGCCCATTGG
AGGAGCAAGCTGCTGGCCAAATACCAGGAGATCCCCTTCTATCACATTTGGAGTGGCAGCCAGAAGGCCCTCCACTGCAC
TTTCACCCTGGAGAGGCACAGCTTGGCCTCCACAGAGCTCACCTGCAAGATCTGCGTGCGGCAAGTGGAAGGGGAGGGCC
AGATATTCCAGCTGCATACCACTCTGGCAGAGACACCTGCTGGCTCCCTGGACACTCTCTGCTCTGCCCCTGGCAGCACT
GTCACCACCCAGCTGGGACCTTATGCCTTCAAGATCCCACTGTCCATCCGCCAGAAGATATGCAACAGCCTAGATGCCCC
CAACTCACGGGGCAATGACTGGCGGATGTTAGCACAGAAGCTCTCTATGGACCGGTACCTGAATTACTTTGCCACCAAAG
CGAGCCCCACGGGTGTGATCCTGGACCTCTGGGAAGCTCTGCAGCAGGACGATGGGGACCTCAACAGCCTGGCGAGTGCC
TTGGAGGAGATGGGCAAGAGTGAGATGCTGGTGGCTGTGGCCACCGACGGGGACTGCTGA

In a search of public sequence databases, the NOV1b nucleic acid sequence, located on chromsome 10 has 1604 of 1895 bases (84%) identical to a gb:GENBANK-ID:RNU87306|acc:U87306.1 mRNA from *Rattus norvegicus* (*Rattus norvegicus* transmembrane receptor Unc5H2 mRNA, complete cds). (E = 0.0) Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV1b polypeptide (SEQ ID NO:4) encoded by SEQ ID NO:3 has 933 amino acid residues and is presented in Table 1D using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV1b has a signal peptide at the first 26 amino acids and is likely to be localized at the plasma membrane with a certainty of 0.5140. In other embodiments, NOV1b is likely to be localized to the microbody (peroxisome) with a certainty of 0.1064, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, or to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV1b is between positions 26 and 27: SQA-GT

Table 1D. Encoded NOV1b protein sequence (SEQ ID NO:4).

```
MGARSGARGALLLALLLCWDPRLSQAGTDSGSEVLPDSFPSAPAEPLPYFLQEPQDAYIVKNKPVELRCRAFPATQIYFK
CNGEWVSQNDHVTQEGLDEATGLRVREVQIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYVRIAYLRKNFDQEPL
GKEVPLDHEVLLQCRPPEGVPVAEVEWLKNEDVIDPTQDTNFLLTIDHNLIIRQARLSDTANYTCVAKNIVAKRRSTTAT
VIVYVNGGWSSWAEWSPCSNRCGRGWQKRTRTCTNPAPLNGGAFCEGQAFQKTACTTICPVDGAWTEWSKWSACSTECAH
WRSRECMAPPPQNGGRDCSGTLLDSKNCTDGLCMQLEASGDAALYAGLVVAIFVVVAILMAVGVVVYRRNCRDFDTDITD
SSAALTGGFHPVNFKTARPSNPQLLHPSVPPDLTASAGIYRGPVYALQDSTDKIPMTNSPLLDPLPSLKVKVYSSSTTGS
GPGLADGADLLGVLPPGTYPSDFARDTHFLHLRSASLGSQQLLGLPRDPGSSVSGTFGCLGGRLSIPGTGVSLLVPNGAI
PQGKFYEMYLLINKAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMPHCAEVSARDWIFQLKTQAHQGHWEEVVTL
DEETLNTPCYCQLEPRACHILLDQLGTYVFTGESYSRSAVKRLQLAVFAPALCTSLEYSLRVYCLEDTPVALKEVLELER
TLGGYLVEEPKPLMFKDSYHNLRLSLHDLPHAHWRSKLLAKYQEIPFYHIWSGSQKALHCTFTLERHSLASTELTCKICV
RQVEGEGQIFQLHTTLAETPAGSLDTLCSAPGSTVTTQLGPYAFKIPLSIRQKICNSLDAPNSRGNDWRMLAQKLSMDRY
LNYFATKASPTGVILDLWEALQQDDGDLNSLASALEEMGKSEMLVAVATDGDC
```

A search of sequence databases reveals that the NOV1b amino acid sequence has 862 of 945 amino acid residues (91%) identical to, and 893 of 945 amino acid residues (94%) similar to, the 945 amino acid residue ptnr:SPTREMBL-ACC:O08722 protein from *Rattus norvegicus* (Rat) (Transmembrane Receptor UNC5H2) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV1b is expressed in at least adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, and/or RACE sources.

The disclosed NOV1a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 1E.

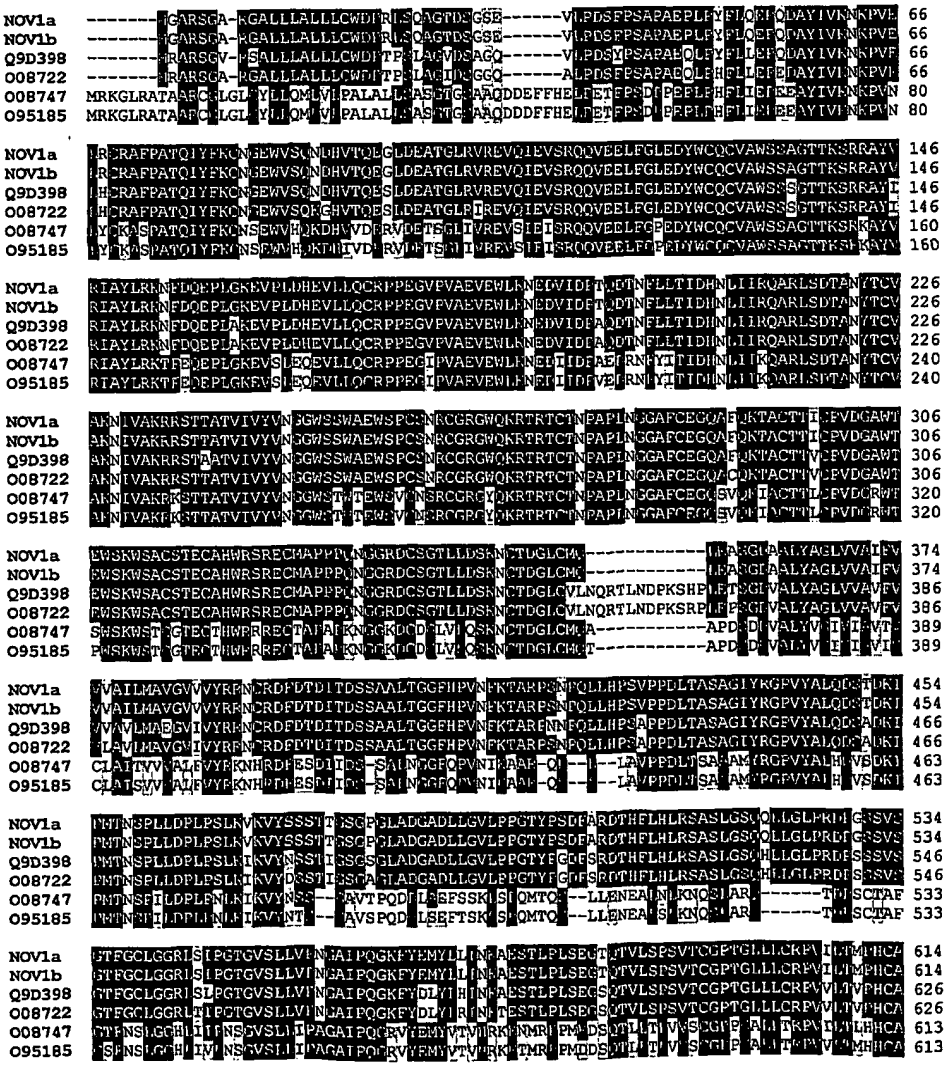
Table 1E. BLAST results for NOV1a

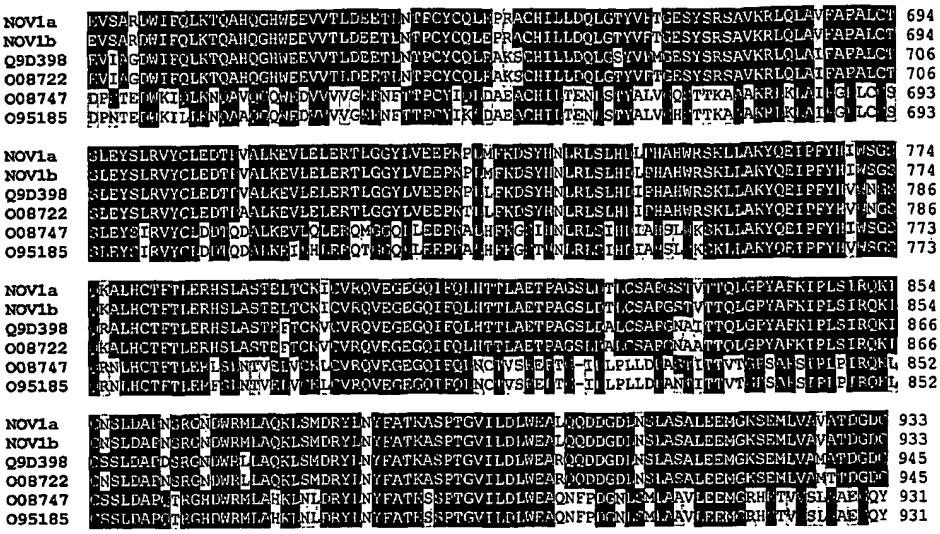
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ptnr:SPTREMBL-ACC:Q9D398	6330415E02RIK PROTEIN - Mus musculus (Mouse)	945	862/945 (91%)	897/945 (94%)	0.0
ptnr:SPTREMBL-ACC:O08722	TRANSMEMBRANE RECEPTOR UNC5H2	945	862/945 (91%)	893/945 (94%)	0.0
ptnr:SPTREMBL-ACC:O08747	UNC-5 HOMOLOG (C. ELEGANS)	931	610/929 (65%)	723/929 (77%)	0.0
ptnr:SPTREMBL-ACC:O95185	TRANSMEMBRANE RECEPTOR UNC5C - Homo sapiens	931	598/929 (64%)	718/929 (77%)	0.0

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 1F. In the ClustalW alignment of the NOV1 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 1F. ClustalW Analysis of NOV1

1) NOV1a (SEQ ID NO:2)
2) NOV1b (SEQ ID NO:4)
3) ptnr: 6330415E02RIK PROTEIN - Mus musculus (Mouse) (SEQ ID NO:33)
4) ptnr: TRANSMEMBRANE RECEPTOR UNC5H2 (SEQ ID NO:34)
5) ptnr: UNC-5 HOMOLOG (C. ELEGANS) (SEQ ID NO:35)
6) ptnr: TRANSMEMBRANE RECEPTOR UNC5C - Homo sapiens (SEQ ID NO:36)





The presence of identifiable domains in NOV1, as well as all other NOVX proteins, was determined by searches using software algorithms such as PROSITE, DOMAIN, Blocks, Pfam, ProDomain, and Prints, and then determining the Interpro number by crossing the domain match (or numbers) using the Interpro website (http:www.ebi.ac.uk/ interpro). DOMAIN results for NOV1 as disclosed in Tables 1G-1O, were collected from the Conserved Domain Database (CDD) with Reverse Position Specific BLAST analyses. This BLAST analysis software samples domains found in the Smart and Pfam collections. For Tables 1G-1O and all successive DOMAIN sequence alignments, fully conserved single residues are indicated by black shading or by the sign (|) and "strong" semi-conserved residues are indicated by grey shading or by the sign (+). The "strong" group of conserved amino acid residues may be any one of the following groups of amino acids: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW.

Tables 1G-1O list the domain descriptions from DOMAIN analysis results against NOV1a. This indicates that the NOV1a sequence has properties similar to those of other proteins known to contain this domain.

Table 1G. Domain Analysis of NOV1a

gnl|Smart|smart00218, ZU5, Domain present in ZO-1 and Unc5-like netrin receptors; Domain of unknown function. (SEQ ID NO:85)
CD-Length = 104 residues, 100.0% aligned
Score = 149 bits (376), Expect = 7e-37

```
Query:  529  PGSSVSGTFGCLGGRLSIPGTGVSLLVPNGAIPQGKFYEMYLLINKAESTLPLSEGTQTV  588
             |   |||||   ||||  | |||  |++|  ||||||   |  ||+++   ||  |  |  +|+
Sbjct:  1    PSFLVSGTFDARGGRLRGPRTGVRLIIPPGAIPQGTRYTCYLVVHDKLSTPPPLEEGETL  60

Query:  589  LSPSVTCGPTGLLLCRPVILTMPHCAEVSARDWIFQLKTQAHQG  632
```

```
                |||  |  |||  |  |   |||||  +||||  +   |||    |     + |
Sbjct:   61    LSPVVECGPHGALFLRPVILEVPHCASLRPRDWEIVLLRSENGG   104
```

Table 1H. Domain Analysis of NOV1a

gnl|Pfam|pfam00791, ZU5, ZU5 domain. Domain present in ZO-1 and Unc5-like netrin receptors Domain of unknown function. (SEQ ID NO:86)
CD-Length = 104 residues, 100.0% aligned
Score = 147 bits (371), Expect = 3e-36

```
Query:   529   PGSSVSGTFGCLGGRLSIPGTGVSLLVPNGAIPQGKFYEMYLLINKAESTLPLSEGTQTV   588
               |  |||||    ||||   | |||  |++| ||||||   |  ||+++    || |  |  +|+
Sbjct:   1     SGFLVSGTFDARGGRLRGPRTGVRLIIPPGAIPQGTRYTCYLVVHDKLSTPPPLEEGETL   60

Query:   589   LSPSVTCGPTGLLLCRPVILTMPHCAEVSARDWIFQLKTQAHQG   632
               |||  |  |||  |  |   |||||  +||||  +   |||    |     + |
Sbjct:   61    LSPVVECGPHGALFLRPVILEVPHCASLRPRDWELVLLRSENGG   104
```

Table 1I. Domain Analysis of NOV1a

gnl|Smart|smart00005, DEATH, DEATH domain, found in proteins involved in cell death (apoptosis).; Alpha-helical domain present in a variety of proteins with apoptotic functions. Some (but not all) of these domains form homotypic and heterotypic dimers. (SEQ ID NO:87)
CD-Length = 96 residues, 99.0% aligned
Score = 64.7 bits (156), Expect = 2e-11

```
Query:   840   GPYAFKIPLSIRQKICNSLDAPNSRGNDWRMLAQKLSM-DRYLNYFATKAS-----PTGV   893
               |  |  +    |+|+   ||  +  |+|||  ||+|| + +  ++   |++        +
Sbjct:   1     PPGAASLTELTREKLAKLLD--HDLGDDWRELARKLGLSEADIDQIETESPRDLAEQSYQ   58

Query:   894   ILDLWEALQQDDGDLNSLASALEEMGKSEMLVAVATD   930
               +|  |||  +  +  | +|  || +||+ + +  + ++
Sbjct:   59    LLRLWEQREGKNATLGTLLEALRKMGRDDAVELLRSE   95
```

Table 1J. Domain Analysis of NOV1a

gnl|Smart|smart00209, TSP1, Thrombospondin type 1 repeats; Type 1 repeats in thrombospondin-1 bind and activate TGF-beta. (SEQ ID NO:88)
CD-Length = 51 residues, 100.0% aligned
Score = 62.4 bits (150), Expect = 1e-10

```
Query:   249   WSSWAEWSPCSNRCGRGWQKRTRTCTNPAPLNGGAFCEGQAFQKTACTT-ICP   300
               |  |+||||||  ||  |  |  |||  |   |||  |  |   +  ||    ||
Sbjct:   1     WGEWSEWSPCSVTCGGGVQTRTRCCNPPP--NGGGPCTGPDTETRACNEQPCP   51
```

Table 1K. Domain Analysis of NOV1a

gnl|Smart|smart00209, TSP1, Thrombospondin type 1 repeats; Type 1 repeats in thrombospondin-1 bind and activate TGF-beta. (SEQ ID NO:88)
CD-Length = 51 residues, 98.0% aligned
Score = 49.3 bits (116), Expect = 1e-06

```
Query:  305  WTEWSKWSACSTECAH-WRSRECMAPPPQNGGRDCSGTLLDSKNCTDGLC  353
Sbjct:  1    WGEWSEWSPCSVTCGGGVQTRTRCCNPPPNGGGPCTGPDTETRACNEQPC  50
```

Table 1L. Domain Analysis of NOV1a

gnl|Pfam|pfam00531, death, Death domain. (SEQ ID NO:89)
CD-Length = 83 residues, 98.8% aligned
Score = 57.4 bits (137), Expect = 4e-09

```
Query:  852  QKICNSLDAPNSRGNDWRMLAQKLSM-DRYLNYFATKA----SPTGVILDLWEALQQDDG  906
Sbjct:  1    RELCKLLDDP--LGRDWRRLARKLGLSEEEIDQIEHENPRLASPTYQLLDLWEQRGGKNA  58

Query:  907  DLNSLASALEEMGKSEMLVAVATD  930
Sbjct:  59   TVGTLLEALRKMGRDDAVELLESA  82
```

Table 1M. Domain Analysis of NOV1a

gnl|Pfam|pfam00090, tsp_1, Thrombospondin type 1 domain. (SEQ ID NO:90)
CD-Length = 48 residues, 91.7% aligned
Score = 49.7 bits (117), Expect = 7e-07

```
Query:  250  SSWAEWSPCSNRCGRGWQKRTRTCTNPAPLNGGAFCEGQAFQKTACT  296
Sbjct:  1    SPWSEWSPCSVTCGKGIRTRQRTCNSPA---GGKPCTGDAQETEACM  44
```

Table 1N. Domain Analysis of NOV1a

gnl|Smart|smart00409, IG, Immunoglobulin (SEQ ID NO:91)
CD-Length = 86 residues, 100.0% aligned
Score = 48.9 bits (115), Expect = 1e-06

```
Query:  159  PLGKEVPLDHEVLLQCRPPEGVPVAEVEWLKNEDVIDPTQDTNFLLTIDHN---LIIRQA  215
Sbjct:  1    PPSVTVKEGESVTLSCEAS-GNPPPTVTWYKQGGKL-LAESGRFSVSRSGGNSTLTISNV  58

Query:  216  RLSDTANYTCVAKNIVAKRRSTTATVIVY  244
Sbjct:  59   TPEDSGTYTCAATNSSGSASSGT-TLTVL  86
```

Table 1O. Domain Analysis of NOV1a

gnl|Smart|smart00408, IGc2, Immunoglobulin C-2 Type (SEQ ID NO:92)
CD-Length = 63 residues, 87.3% aligned
Score = 42.7 bits (99), Expect = 9e-05

```
Query:  170  VLLQCRPPEGVPVAEVEWLKNEDVIDPTQDTNFLLTIDHNLIIRQARLSDTANYTCVAKN  229
             | | | |  | ||  + |||+   +  ++    ++     | |+   | |+  |||||+|
Sbjct:  6    VTLTC-PASGDPVPNITWLKDGKPLPESR----VVASGSTLTIKNVSLEDSGLYTCVARN  60
```

Migration of neurons from proliferative zones to their functional sites is fundamental to the normal development of the central nervous system. Disruption of the mouse rostral cerebellar malformation mutation (rcm) gene, also called the Unc5h3 gene, resulted in a failure of tangentially migrating granule cells to recognize the rostral boundary of the cerebellum. In rcm-mutant mice, the cerebellum is smaller and has fewer folia than in wildtype, ectopic cerebellar cells are present in midbrain regions by 3 days after birth, and there are abnormalities in postnatal cerebellar-neuronal migration. Ackerman et al. (1997). Sequence analysis has revealed that the predicted rcm mouse protein is a transmembrane protein that contains 2 immunoglobulin (Ig)-like domains and 2 type I thrombospondin (THBS1) motifs in the extracellular region. Ig and THBS1 domains are also found in the extracellular region of the C. elegans UNC5 transmembrane protein, and the C-terminal 865-amino acid region of Rcm is 30% identical to UNC5. In addition, the UNC5 protein is essential for dorsal guidance of pioneer axons and for the movement of cells away from the netrin ligand. Ackerman et al. (1997). In the developing brain of vertebrates, netrin-1 plays a role in both cell migration and axonal guidance.

In the developing nervous system, migrating cells and axons are guided to their targets by cues in the extracellular environment. The netrins are a family of phylogenetically conserved guidance cues that can function as diffusible attractants and repellents for different classes of cells and axons. In vertebrates, insects and nematodes, members of the DCC subfamily of the immunoglobulin superfamily have been implicated as receptors that are involved in migration towards netrin sources. In Caenorhabditis elegans, the transmembrane protein UNC-5 has been implicated in these responses, as loss of UNC-5 function causes migration defects and ectopic expression of UNC-5 in some neurons can redirect their axons away from a netrin source.

The disclosed NOV1 nucleic acid of the invention encoding a UNC5H2-like protein includes the nucleic acid whose sequence is provided in Table 1A, 1C or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 1A or 1C while still encoding a protein

that maintains its UNC5H2 like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 16 percent of the bases may be so changed.

The disclosed NOV1 protein of the invention includes the UNC5H2-like protein whose sequence is provided in Table 1B or 1D. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 1B or 1D while still encoding a protein that maintains its UNC5H2-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 9 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this UNC5H2-like protein (NOV1) may function as a member of a "UNC5H2 family". Therefore, the NOV1 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV1 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the UNC5H2-like protein (NOV1) may be useful in gene therapy, and the UNC5H2 -like protein (NOV1) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering

from cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, cancers, and/or other pathologies and disorders. For example, a cDNA encoding the transmembrane receptor UNC5H2-like protein may be useful in transmembrane receptor UNC5H2 therapy, and the transmembrane receptor UNC5H2-like protein may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, cancers, and other diseases, disorders and conditions of the like. Also since this gene is expressed at a measurably higher level in several cancer cell lines (including breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer and pancreatic cancer), it may be useful in diagnosis and treatment of these cancers. The NOV1 nucleic acid encoding the UNC5H2-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV1 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV1 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies"

section below. The disclosed NOV1 proteins have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV1 epitope is from about amino acids 1 to 100. In another embodiment, a NOV1 epitope is from about amino acids 200 to 300. In further embodiments, a NOV1 epitope is from about amino acids 450 to 500, from about amino acids 600 to 900, from about amino acids 950 to 1000, from about amino acids 1200 to 1300, from about amino acids 1400 to 1600, from about amino acids 1800 to 1900, from about amino acids 1950 to 2050, and from about amino acids 2200 to 2300. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV2

NOV2 includes three novel protein tyrosine phosphatase precursor-like proteins disclosed below. The disclosed sequences have been named NOV2a, NOV2b, and NOV2c.

NOV2a

A disclosed NOV2a nucleic acid of 6994 nucleotides (also referred to as SC126422078_A) encoding a receptor protein tyrosine phosphatase precursor-like protein is shown in Table 2A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 31-33 and ending with a TAA codon at nucleotides 6874-6876. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 2A. The start and stop codons are in bold letters.

Table 2A. NOV2a nucleotide sequence (SEQ ID NO:5).

TGATTCTACTGGCTGAAAAATGTAATAAAG**ATG**GATTTTCTTATCATTTTTCTTTTACTTTTTATTGGGACT
TCAGAGACACAGGTAGATGTTTCCAATGTCGTTCCTGGTACTAGGTACGATATAACCATCTCTTCAATTTCT
ACAACATACACCTCACCTGTTACTAGAATAGGGGCTTCTAATGAACCAGGGCCTCCAGTCTTCCTAGCCGGG
GAAAGAGTCGGATCTGCTGGGATTCTTCTGTCTTGGAATACACCACCTAATCCAAATGGAAGGATTATATCT
TACATTGTCAAATATAAGGAAGTTTGTCCGTGGATGCAAACAGTATATACACAAGTCAGATCAAAGCCAGAC
AGTCTGGAAGTTCTTCTTACTAATCTTAATCCTGGAACAACATATGAAATTAAGGTAGCTGCTGAAAACAGT
GCTGGCATTGGAGTGTTTAGTGATCCATTTCTCTTCCAAACTGCAGAAAGTGCTCCAGGAAAAGTGGTGGAT
TTCACAGGTGAGGCTGTCCCGTTCAGCAGTAAGCTGATGTGGTATACCTCGGCAACCAAAAAAAAAATTACC
AGCTTCAAGATTAGTGTCAAGCATAACAGAAGTGGGATAGTAGTGAAAGAAGTGTCAATCAGAGTGGAGTGC
ATTTTAAGTGCTTCCCTTCCTTTGCACTGCAACGAGAATAGTGAATCTTTTTTATGGAGTACAGCCAGCCCT
TCTCCAACCCTTGGTAGAGTTACACCTCCATCGCGTACCACACATTCATCAAGCACGTTGACACAGAATGAG
ATCAGCTCTGTGAAAGAGCCTATCAGTTTTGTAGTGACACACTTGAGACCTTATACAACATATCTTTTTGAA
GTTTCAGCTGCTACAACTGAAGCAGGTTATATTGATAGTACGATTGTCAGAACACCAGAATCAGTGCCTGAA
GGACCACCACAAAACTGCGTAACAGGCAACATCACAGGAAAGTCCTTTTCAATTTTATGGGACCCACCAACT
ATAGTAACAGGGAAATTTAGTTATAGAGTTGAATTATATGGACCATCAGCAGGTCGCATTTTGGATAACAGC
ACAAAAGACCTCAAGTTTGCATTCACTAACCTAACACCATTTACAATGTATGATGTCTATATTGCGGCTGAA
ACCAGTGCAGGGACTGGGCCCAAGTCAAATATTTCAGTATTCACTCCACCAGATGTTCCAGGGGCAGTGTTT
GATTTACAACTTGCAGAGGTAGAATCCACGCAAGTAAGAATTACTTGGAAGAAACCACGACAACCAAATGGA
ATTATTAACCAATACCGAGTGAAAGTGCTAGTTCCAGAGACAGGAATAATTTTGGAAAATACTTTGCTCACT

GGAAATAATGAGATAAATGACCCCATGGCTCCAGAAATTGTGAACATAGTACAGCCAATGGTAGGATTATAT
GAGGGTTCAGCAGAGATGTCGTCTGACCTTCACTCACTTGCTACATTTATATATAACAGCCATCCAGATAAA
AACTTTCCTGCAAGGAATAGAGCTGAAGACCAGACTTCACCAGTTGTAACTACAAGGAATCAGTATATTACT
GACATTGCAGCTGAACAGCTGACTTATGTTCTTATCAGATTAAGGAGATTTTGGGCTGAGACAATGGGGTTT
TCTAGATATACAATCATGTCATCTGCAAGCAGGGACAATTTGACTTCCCCAGGCCCTTTGTCAGCCCAAAAT
TTCAGAGTTACACATGTTACCATAACAGAAGTATTTTTACACTGGGATCCTCCAGATCCTGTATTTTTTCAT
CATTACCTTATCACTATTTTGGATGTTGAAAACCAATCCAAGAGTATTATTTTAAGGACATTAAACAGTTTG
TCTCTTGTCCTTATAGGGTTAAAGAAATACACAAAATACAAAATGAGAGTGGCAGCCTCAACCCACGTTGGA
GAAAGTTCTTTGTCTGAAGAAAATGACATCTTTGTGAGAACTTCAGAAGATGAACCGGAATCATCACCTCAA
GATGTCGAAGTAATTGATGTTACCGCAGATGAAATAAGGTTGAAGTGGTCACCACCCGAAAAGCCCAATGGG
ATCATTATTGCTTATGAAGTGCTATATAAAAATATAGATACTTTATATATGAAGAACACATCAACAACAGAC
ATAATATTAAGGAACTTAAGACCTCACACCCTCTATAACATTTCTGTAAGGTCTTACACCAGATTTGGTCAT
GGCAATCAGGTATCTTCTTTACTCTCTGTAAGGACTTCGGAGTCAGTGCCTGATAGTGCACCAGAAAATATC
ACTTACAAAAATATTTCTTCTGGAGAGATTGAGCTATCATTCCTTCCCCCAAGTAGTCCCAATGGAATCATA
CAAAAATATACAATTTATCTCAAGAGAAGTAATGGAAATGAGGAAAGAACTATAAATACAACCTCTTTAACC
CAAAACATTAAAGGTCTGAAGAAATATACCCAATATATCATTGAGGTGTCTGCTAGTACACTCAAAGGTGAA
GGAGTTCGGAGTGCTCCCATAAGTATACTGACGGAGGAAGATGCTCCTGATTCTCCCCCTCAAGACTTCTCT
GTAAAACAGTTGTCTGGTGTCACGGTGAAGTTGTCATGGCAACCACCCCTGGAGCCAAATGGAATTATCCTT
TATTACACAGTTTATGTCTGGAGATCATCATTAAAAACTATTAATGTCACTGAAACATCATTGGAGTTATCA
GATTTGGATTATAATGTTGAATACAGTGCTTATGTAACAGCTAGCACCAGATTTGGTGATGGGAAAACAAGA
AGCAATATCATTAGCTTTCAAACACCAGAGGGACCAAGCGATCCTCCCAAAGATGTTTATTATGCAAACCTC
AGTTCTTCATCAATAATTCTTTTCTGGACACCTCCTTCAAAACCTAATGGGATTATACAATATTACTCTGTT
TATTACAGAAATACTTCAGGTACTTTTATGCAGAATTTTACACTCCATGAAGTAACCAATGACTTTGACAAT
ATGACTGTATCCACAATTATAGATAAACTGACAATATTCAGCTACTATACATTTTGGTTAACAGCAAGTACT
TCAGTTGGAAATGGGAATAAAAGCAGTGACATCATTGAAGTATACACAGATCAAGACGTACCTGAAGGGTTT
GTTGGAAACCTGACTTACGAATCCATTTCGTCAACTGCAATAAATGTAAGCTGGGTCCCACCGGCTCAACCA
AACGGTCTAGTCTTCTACTATGTTTCACTGATCTTACAGCAGACTCCTCGCCATGTGAGACCACCTCTTGTT
ACATATGAGAGAAGCATATATTTTGATAATCTGGAAAAATACACTGATTATATATTAAAAATTACTCCATCA
ACAGAAAAGGGATTCTCTGATACCTATACTGCCCAGCTATACATCAAGACTGAAGAAGATATCCCAGAAACT
TCACCAATAATCAACACTTTTAAAAACCTTTCCTCTACCTCAGTTCTCTTATCATGGGATCCCCCAGTAAAG
CCAAATGGTGCAATAATAAGTTATGATTTAACTTTACAAGGACCAAATGAAAATTATTCTTTCATTACTTCT
GATAATTACATAATATTGGAAGAGCTTTCACCATTTACATTATATAGCTTTTTTGCTGCCGCAAGAACTAGA
AAAGGACTTGGTCCTTCCAGTATTCTTTTCTTTTACACAGATGAGTCAGTGCCGTTAGCACCTCCACAAAAT
TTGACTTTAATCAACTGTACTTCAGACTTTGTATGGCTGAAATGGAGCCCAAGTCCTCTTCCAGGTGGTATT
GTTAAAGTATATAGTTTTAAAATTCATGAACATGAAACTGACACTATATATTATAAGAATATATCAGGATTT
AAAACTGAAGCCAAACTTGTTGGACTGGAACCAGTCAGCACCTACTCTATCCGTGTATCTGCGTTCACCAAA
GTTGGAAATGGCAATCAATTTAGTAATGTAGTAAAATTCACAACCCAAGAATCAGTTCCAGATGTCGTGCAG
AATATGCAGTGCATGGCAACTAGCTGGCAGTCAGTTTTAGTGAAATGGGATCCACCCAAAAAGGCAAATGGA
ATAATAACGCAGTATATGGTAACAGTTGAAAGGAATTCTACAAAAGTTTCTCCCCAAGATCACATGTACACT
TTCATAAAGCTTCTTGCCAATACCTCATATGTCTTTAAAGTAAGAGCTTCAACCTCAGCTGGTGAAGGTGAT
GAAAGCACATGCCATGTCAGCACACTACCTGAAACAGTTCCCAGTGTTCCCACAAATATTGCTTTTTCTGAT
GTTCAGTCAACTAGTGCAACATTGACATGGATAAGACCTGACACTATCCTTGGCTACTTTCAAAATTACAAA
ATTACCACTCAACTTCGTGCTCAAAAATGCAAAGAATGGGAATCCGAAGAATGTGTTGAATATCAAAAAATT
CAATACCTCTATGAAGCTCACTTAACTGAAGAGACAGTATATGGATTAAAGAAATTTAGATGGTATAGATTC
CAAGTGGCTGCCAGCACCAATGCTGGCTATGGCAATGCTTCAAACTGGATTTCTACAAAAACTCTGCCTGGC
CCTCCAGATGGTCCTCCTGAAAATGTTCATGTAGTAGCAACATCACCTTTTAGCATCAGCATAAGCTGGAGT
GAACCTGCTGTCATTACTGGACCAACATGTTATCTGATTGATGTCAAATCGGTAGATAATGATGAATTTAAT
ATATCCTTCATCAAGTCAAATGAAGAAAATAAAACCATAGAAATTAAAGATTTAGAAATATTCACAAGGTAT
TCTGTAGTGATCACTGCATTTACTGGGAACATTAGTGCTGCATATGTAGAAGGGAAGTCAAGTGCTGAAATG
ATTGTTACTACTTTAGAATCAGCCCCAAAGGACCCACCTAACAACATGACATTTCAGAAGATACCAGATGAA
GTTACAAAATTTCAATTAACGTTCCTTCCTCCTTCTCAACCTAATGGAAATATCCAAGTATATCAAGCTCTG
GTTTACCGAGAAGATGATCCTACTGCTGTCCAGATTCACAACCTCAGTATTATACAGAAAACCAACACATTC
GTCATTGCAATGCTAGAAGGACTAAAAGGTGGACATACATACAATATCAGTGTTTACGCAGTCAATAGTGCT
GGTGCAGGTCCAAAGGTTCCGATGAGAATAACCATGGATATCAAAGCTCCAGCACGACCAAAAACCAAACCA
ACCCCTATTTATGATGCCACAGGAAAACTGCTTGTGACTTCAACAACAATTACAATCAGAATGCCAATATGT
TACTACAGTGATGATCATGGACCAATAAAAAATGTACAAGTGCTTGTGACAGAAACAGGAGCTCAGCATGAT
GGAAATGTAACAAAGTGGTATGATGCATATTTTAATAAAGCAAGGCCATATTTTACAAATGAAGGCTTTCCT
AACCCTCCATGTACAGAAGGAAAGACAAAGTTTAGTGGCAATGAAGAAATCTACATCATAGGTGCTGATAAT
GCATGCATGATTCCTGGCAATGAAGACAAAATTTGCAATGGACCACTGAAACCAAAAAAGCAATACTTATTT
AAATTTAGAGCTACAAATATTATGGGACAATTTACTGACTCTGATTATTCTGACCCTGTTAAGACTTTAGGC
GAAGGACTTTCAGAAAGAACCGTAGAGATCATTCTTTCCGTCACTTTGTGTATCCTTTCAATAATTCTCCTT
GGAACAGCTATTTTTGCATTTGCAAGAATTCGACAGAAGCAGAAAGAAGGTGGCACATACTCTCCTCAGGAT
GCAGAAATTATTGACACTAAATTGAAGCTGGATCAGCTCATCACAGTGGCAGACCTGGAACTGAAGGACGAG
AGATTAACGCGGCCAATAAGCAAGAAATCCTTCCTGCAACATGTTGAAGAGCTTTGCACAAACAACAACCTA
AAGTTTCAAGAAGAATTTTCGGAATTACCAAAATTTCTTCAGGATCTTTCTTCAACTGATGCTGATCTGCCT
TGGAATAGAGCAAAAAACCGCTTCCCAAACATAAAACCATATAATAATAACAGAGTAAAGCTGATAGCTGAC
GCTAGTGTTCCAGGTTCGGATTATATTAATGCCAGCTATATTTCTGGTTATTTATGTCCAAATGAATTTATT
GCTACTCAAGGTCCACTACCAGGAACAGTTGGAGATTTTTGGAGAATGGTGTGGGAAACCAGAGCAAAAACA
TTAGTAATGCTAACACAGTGTTTTGAAAAAGGACGGATCAGATGCCATCAGTATTGGCCAGAGGACAACAAG

CCAGTTACTGTCTTTGGAGATATAGTGATTACAAAGCTAATGGAGGATGTTCAAATAGATTGGACTATCAGG
GATCTGAAAATTGAAAGGCATGGGGATTGCATGACTGTTCGACAGTGTAACTTTACTGCCTGGCCAGAGCAT
GGGGTTCCTGAGAACAGCGCCCCTCTAATTCACTTTGTGAAGTTGGTTCGAGCAAGCAGGGCACATGACACC
ACACCTATGATTGTTCACTGCAGTGCTGGAGTTGGAAGAACTGGAGTTTTTATTGCTCTGGACCATTTAACA
CAACATATAAATGACCATGATTTTGTGGATATATATGGACTAGTAGCTGAACTGAGAAGTGAAAGAATGTGC
ATGGTGCAGAATCTGGCACAGTATATCTTTTTACACCAGTGCATTCTGGATCTCTTATCAAATAAGGGAAGT
AATCAGCCCATCTGTTTTGTTAACTATTCAGCACTTCAGAAGATGGACTCTTTGGACGCCATGGAAGGTGGT
GATGTTGAGCTTGAATGGGAAGAAACCACTATGTAAATATTCAGACCAAAGGATACAATTGGAAGAGATTTT
TAAATCCCAGGGGCCAAAGTTACCCCCTCATTCTTCCGAATTGAAATGTGCAACCTTAAAGAAATATCTATG
CTTCTCTCAC

In a search of public sequence databases, the NOV2a nucleic acid sequence, located on chromsome 12 has 777 of 3293 bases (84%) identical to a gb:GENBANK-ID:AF063249|acc:AF063249.1 mRNA from *Rattus norvegicus* (*Rattus norvegicus* glomerular mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete cds) (E = 0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV2a polypeptide (SEQ ID NO:6) encoded by SEQ ID NO:5 has 2281 amino acid residues and is presented in Table 2B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV2a has a signal peptide and is likely to be localized in the plasma membrane with a certainty of 0.4600. In other embodiments, NOV2a may also be localized to the microbody (peroxisome) with acertainty of 0.1381, the endoplasmic reticulum (membrane) with a certainty of 0.1000 or in the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for a NOV2a peptide is between amino acids 17 and 18, at: SET-QV.

Table 2B. Encoded NOV2a protein sequence (SEQ ID NO:6).

MDFLIIFLLLFIGTSETQVDVSNVVPGTRYDITISSISTTYTSPVTRIGASNEPGPPVFLAGERVGSAGILL
SWNTPPNPNGRIISYIVKYKEVCPWMQTVYTQVRSKPDSLEVLLTNLNPGTTYEIKVAAENSAGIGVFSDPF
LFQTAESAPGKVVDFTGEAVPFSSKLMWYTSATKKKITSFKISVKHNRSGIVVKEVSIRVECILSASLPLHC
NENSESFLWSTASPSPTLGRVTPPSRTTHSSSTLTQNEISSVKEPISFVVTHLRPYTTYLFEVSAATTEAGY
IDSTIVRTPESVPEGPPQNCVTGNITGKSFSILWDPPTIVTGKFSYRVELYGPSAGRILDNSTKDLKFAFTN
LTPFTMYDVYIAAETSAGTGPKSNISVFTPPDVPGAVFDLQLAEVESTQVRITWKKPRQPNGIINQYRVKVL
VPETGIILENTLLTGNNEINDPMAPEIVNIVQPMVGLYEGSAEMSSDLHSLATFIYNSHPDKNFPARNRAED
QTSPVVTTRNQYITDIAAEQLTYVLIRLRRFWAETMGFSRYTIMSSASRDNLTSPGPLSAQNFRVTHVTITE
VFLHWDPPDPVFFHHYLITILDVENQSKSIILRTLNSLSLVLIGLKKYTKYKMRVAASTHVGESSLSEENDI
FVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEKPNGIIIAYEVLYKNIDTLYMKNTSTTDIILRNLRPHT
LYNISVRSYTRFGHGNQVSSLLSVRTSESVPDSAPENITYKNISSGEIELSFLPPSSPNGIIQKYTIYLKRS
NGNEERTINTTSLTQNIKGLKKYTQYIIEVSASTLKGEGVRSAPISILTEEDAPDSPPQDFSVKQLSGVTVK
LSWQPPLEPNGIILYYTVYVWRSSLKTINVTETSLELSDLDYNVEYSAYVTASTRFGDGKTRSNIISFQTPE
GPSDPPKDVYYANLSSSSIILFWTPPSKPNGIIQYYSVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIIDKL
TIFSYYTFWLTASTSVGNGNKSSDIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVPPAQPNGLVFYYVSL
ILQQTPRHVRPPLVTYERSIYFDNLEKYTDYILKITPSTEKGFSDTYTAQLYIKTEEDIPETSPIINTFKNL
SSTSVLLSWDPPVKPNGAIISYDLTLQGPNENYSFITSDNYIILEELSPFTLYSFFAAARTRKGLGPSSILF
FYTDESVPLAPPQNLTLINCTSDFVWLKWSPSPLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVGLE
PVSTYSIRVSAFTKVGNGNQFSNVVKFTTQESVPDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMVTVE
RNSTKVSPQDHMYTFIKLLANTSYVFKVRASTSAGEGDESTCHVSTLPETVPSVPTNIAFSDVQSTSATLTW
IRPDTILGYFQNYKITTQLRAQKCKEWESEECVEYQKIQYLYEAHLTEETVYGLKKFRWYRFQVAASTNAGY
GNASNWISTKTLPGPPDGPPENVHVVATSPFSISISWSEPAVITGPTCYLIDVKSVDNDEFNISFIKSNEEN
KTIEIKDLEIFTRYSVVITAFTGNISAAYVEGKSSAEMIVTTLESAPKDPPNNMTFQKIPDEVTKFQLTFLP
PSQPNGNIQVYQALVYREDDPTAVQIHNLSIIQKTNTFVIAMLEGLKGGHTYNISVYAVNSAGAGPKVPMRI

TMDIKAPARPKTKPTPIYDATGKLLVTSTTITIRMPICYYSDDHGPIKNVQVLVTETGAQHDGNVTKWYDAY
FNKARPYFTNEGFPNPPCTEGKTKFSGNEEIYIIGADNACMIPGNEDKICNGPLKPKKQYLFKFRATNIMGQ
FTDSDYSDPVKTLGEGLSERTVEIILSVTLCILSIILLGTAIFAFARIRQKQKEGGTYSPQDAEIIDTKLKL
DQLITVADLELKDERLTRPISKKSFLQHVEELCTNNNLKFQEEFSELPKFLQDLSSTDADLPWNRAKNRFPN
IKPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGPLPGTVGDFWRMVWETRAKTLVMLTQCFEK
GRIRCHQYWPEDNKPVTVFGDIVITKLMEDVQIDWTIRDLKIERHGDCMTVRQCNFTAWPEHGVPENSAPLI
HFVKLVRASRAHDTTPMIVHCSAGVGRTGVFIALDHLTQHINDHDFVDIYGLVAELRSERMCMVQNLAQYIF
LHQCILDLLSNKGSNQPICFVNYSALQKMDSLDAMEGGDVELEWEETTM

A search of sequence databases reveals that the NOV2a amino acid sequence has 1894 of 2301 amino acid residues (82%) identical to, and 2078 of 2301 amino acid residues (90%) similar to, the 2302 amino acid residue ptnr:SPTREMBL-ACC:O88488 protein from *Rattus norvegicus* (Rat) (Glomerular Mesangial Cell Receptor Protein-Tyrosine Phosphatase Precursor (EC 3.1.3.48)) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV2 is expressed in at least kidney and colon. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

In addition, the sequence is predicted to be expressed in *Rattus norvegicus* :kidney because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF063249|acc:AF063249.1) a closely related Rattus norvegicus glomerular mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete cds homolog.

NOV2b

A disclosed NOV2b nucleic acid of 2565 nucleotides (also referred to as CG50718-02) encoding a novel Glomerular Mesangial Cell Receptor Protein-Tyrosine-like protein is shown in Table 2C. An open reading frame was identified beginning with an AGA codon at nucleotides 1-3 and ending with a GAG codon at nucleotides 2563-2565. The start and stop codons are in bold letters in Table 2C. Because the first and last codons are not traditional initiation and termination codons, NOV2b could represent a partial reading frame that extends in the 5' and/or 3' directions.

Table 2C. NOV2b nucleotide sequence (SEQ ID NO:7).

AGATCTCCTGAAGGGTTTGTTGGAAACCTGACTTACGAATCCATTTCGTCAACTGCAATAAATGTAAGCTGG
GTCCCACCGGCTCAACCAAACGGTCTAGTCTTCTACTATGTTTCACTGATCTTACAGCAGACTCCTCGCCAT
GTGAGACCACCTCTTGTTACATATGAGAGAAGCATATATTTTGATAATCTGGAAAAATACACTGATTATATA
TTAAAAATTACTCCATCAACAGAAAAGGGATTCTCTGATACCTATACTGCCCAGCTATACATCAAGACTGAA
GAAGATGTCCCAGAAACTTCACCAATAATCAACACTTTTAAAAACCTTTCCTCTACCTCAGTTCTCTTATCA
TGGGATCCCCCAGTAAAGCCAAATGGTGCAATAATAAGTTATGATTTAACTTTACAAGGACCAAATGAAAAT
TATTCTTTCATTACTTCTGATAATTACATAATATTGGAAGAGCTTTCACCATTTACATTATATAGCTTTTTT
GCTGCCGCAAGAACTAGAAAAGGACTTGGTCCTTCCAGTATTCTTTTCTTTTACACAGATGAGTCAGTGCCG

TTAGCACCTCCACAAAATTTGACTTTAATCAACTGTACTTCAGACTTTGTATGGCTGAAATGGAGCCCAAGT
CCTCTTCCAGGTGGTATTGTTAAAGTATATAGTTTTAAAATTCATGAACATGAAACTGACACTATATATTAT
AAGAATATATCAGGATTTAAAACTGAAGCCAAACTTGTTGGACTGGAACCAGTCAGCACCTACTCTATCCGT
GTATCTGCGTTCACCAAAGTTGGAAATGGCAATCAATTTAGTAATGTAGTAAAATTCACAACCCAAGAATCA
GTTCCAGATGTCGTGCAGAATATGCAGTGCATGGCAACTAGCTGGCAGTCAGTTTTAGTGAAATGGGATCCA
CCCAAAAAGGCAAATGGAATAATAACGCAGTATATGGTAACAGTTGAAAGGAATTCTACAAAAGTTTCTCCC
CAAGATCACATGTACACTTTCATAAAGCTTCTTGCCAATACCTCATATGTCTTTAAAGTAAGAGCTTCAACC
TCAGCTGGTGAAGGTGATGAAAGCACATGCCATGTCAGCACACTACCTGAAACAGTTCCCAGTGTTCCCACA
AATATTGCTTTTTCTGATGTTCAGTCAACTAGTGCAACATTGACATGGATAAGACCTGACACTATCCTTGGC
TACTTTCAAAATTACAAAATTACCACTCAACTTCGTGCTCAAAAATGCAAAGAATGGGAATCCGAAGAATGT
GTTGAATATCAAAAAATTCAATACCTCTATGAAGCTCACTTAACTGAAGAGACAGTATATGGATTAAAGAAA
TTTAGATGGTATAGATTCCAAGTGGCTGCCAGCACCAATGCTGGCTATGGCAATGCTTCAAACTGGATTTCT
ACAAAAACTCTGCCTGGCCCTCCAGATGGTCCTCCTGAAAATGTTCATGTAGTAGCAACATCACCTTTTAGC
ATCAGCATAAGCTGGAGTGAACCTGCTGTCATTACTGGACCAACATGTTATCTGATTGATGTCAAATCGGTA
GATAATGATGAATTTAATATATCCTTCATCAAGTCAAATGAAGAAAATAAAACCATAGAAATTAAAGATTTA
GAAATATTCACAAGGTATTCTGTAGTGATCACTGCATTTACTGGGAACATTAGTGCTGCATATGTAGAAGGG
AAGTCAAGTGCTGAAATGATTGTTACTACTTTAGAATCAGCCCCAAAGGACCCACCTAACAACATGACATTT
CAGAAGATACCAGATGAAGTTACAAAATTTCAATTAACGTCCCTTCCTCCTTCTCAACCTAATGGAAATATC
CAAGTATATCAAGCTCTGGTTTACCGAGAAGATGATCCTACTGCTGTCCAGATTCACAACCTCAGTATTATA
CAGAAAACCAACACATTCGTCATTGCAATGCTAGAAGGACTAAAAGGTGGACATACATACAATATCAGTGTT
TACGCAGTCAATAGTGCTGGTGCAGGTCCAAAGGTTCCGATGAGAATAACCATGGATATCAAAGCTCCAGCA
CGACCAAAAACCAAACCAACCCCTATTTATGATGCCACAGGAAAACTGCTTGTGACTTCAACAACAATTACA
ATCAGAATGCCAATATGTTACTACAGTGATGATCATGGACCAATAAAAAATGTACAAGTGCTTGTGACAGAA
ACAGGAGCTCAGCATGATGGAAATGTAACAAAGTGGTATGATGCATATTTTAATAAAGCAAGGCCATATTTT
ACAAATGAAGGCTTTCCTAACCCTCCATGTACAGAAGGAAAGACAAAGTTTAGTGGCAATGAAGAAATCTAC
ATCATAGGTGCTGATAATGCATGCATGATTCCTGGCAATGAAGACAAAATTTGCAATGGACCACTGAAACCA
AAAAAGCAATACTTATTTAAATTTAGAGCTACAAATATTATGGGACAATTTACTGACTCTGATTATTCTGAC
CCTGTTAAGACTTTAGGCGAAGGACTTTCAGAAAGAACCCTCGAG

The disclosed NOV2b polypeptide (SEQ ID NO:8) encoded by SEQ ID NO:7 has 855 amino acid residues and is presented in Table 2D using the one-letter amino acid code.

Table 2D. Encoded NOV2b protein sequence (SEQ ID NO:8).

RSPEGFVGNLTYESISSTAINVSWVPPAQPNGLVFYYVSLILQQTPRHVRPPLVTYERSIYFDNLEKYTDYI
LKITPSTEKGFSDTYTAQLYIKTEEDVPETSPIINTFKNLSSTSVLLSWDPPVKPNGAIISYDLTLQGPNEN
YSFITSDNYIILEELSPFTLYSFFAAARTRKGLGPSSILFFYTDESVPLAPPQNLTLINCTSDFVWLKWSPS
PLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVGLEPVSTYSIRVSAFTKVGNGNQFSNVVKFTTQES
VPDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMVTVERNSTKVSPQDHMYTFIKLLANTSYVFKVRAST
SAGEGDESTCHVSTLPETVPSVPTNIAFSDVQSTSATLTWIRPDTILGYFQNYKITTQLRAQKCKEWESEEC
VEYQKIQYLYEAHLTEETVYGLKKFRWYRFQVAASTNAGYGNASNWISTKTLPGPPDGPPENVHVVATSPFS
ISISWSEPAVITGPTCYLIDVKSVDNDEFNISFIKSNEENKTIEIKDLEIFTRYSVVITAFTGNISAAYVEG
KSSAEMIVTTLESAPKDPPNNMTFQKIPDEVTKFQLTSLPPSQPNGNIQVYQALVYREDDPTAVQIHNLSII
QKTNTFVIAMLEGLKGGHTYNISVYAVNSAGAGPKVPMRITMDIKAPARPKTKPTPIYDATGKLLVTSTTIT
IRMPICYYSDDHGPIKNVQVLVTETGAQHDGNVTKWYDAYFNKARPYFTNEGFPNPPCTEGKTKFSGNEEIY
IIGADNACMIPGNEDKICNGPLKPKKQYLFKFRATNIMGQFTDSDYSDPVKTLGEGLSERTLE

NOV2b is expressed in Brain, Colon, Fetal brain, Germ Cell, Heart, Kidney, Prostate, Uterus, brain, breast, colon, kidney, lung.

NOV2c

A disclosed NOV2c nucleic acid of 6903 nucleotides (also referred to as CG50718-05) encoding a novel Glomerular Mesangial Cell Receptor Protein-Tyrosine Phosphatase Precursor-like protein is shown in Table 2E. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 1-3 and ending with a TGA codon at nucleotides

6901-6903. A putative untranslated regions upstream from the initiation codon and downstream of the termination codon are underlined in Table 2E. The start and stop codons are in bold letters.

Table 2E. NOV2c nucleotide sequence (SEQ ID NO:9).

ATGGATTTTCTTATCATTTTTCTTTTACTTTTTATTGGGACTTCAGAGACACAGGTAGATGTTTCCAATGTC
GTTCCTGGTACTAGGTACGATATAACCATCTCTTCAATTTCTACAACATACACCTCACCTGTTACTAGAATA
GTGACAACAAATGTAACAGAACCAGGGCCTCCAGTCTTCCTAGCCGGGGAAAGAGTCGGATCTGCTGGGATT
CTTCTGTCTTGGAATACACCACCTAATCCAAATGGAAGGATTATATCTTACATTGTCAAATATAAGGAAGTT
TGTCCGTGGATGCAAACAGTATATACACAAGTCAGATCAAAGCCAGACAGTCTGGAAGTTCTTCTTACTAAT
CTTAATCCTGGAACAACATATGAAATTAAGGTAGCTGCTGAAAACAGTGCTGGCATTGGAGTGTTTAGTGAT
CCATTTCTCTTCCAAACTGCAGAAAGTCCAGCTCCAGGAAAAGTGGTGAATCTCACAGTTGAGGCCTACAAC
GCTTCAGCAGTTAAGCTGATTTGGTATTTACCTCGGCAACCAAATGGCAAAATTACCAGCTTCAAGATTAGT
GTCAAGCATGCCAGAAGTGGGATAGTAGTGAAAGATGTCTCAATCAGAGTAGAGGACATTTTGACTGGGAAA
TTGCCAGAATGCAATGTAGAGAATAGTGAATCTTTTTTATGGAGTACAGCCAGCCCTTCTCCAACCCTTGGT
AGAGTTACACCTCCATCGCGTACCACACATTCATCAAGCACGTTGACACAGAATGAGATCAGCTCTGTGTGG
AAAGAGCCTATCAGTTTTGTAGTGACACACTTGAGACCTTATACAACATATCTTTTTGAAGTTTCAGCTGCT
ACAACTGAAGCAGGTTATATTGATAGTACGATTGTCAGAACACCAGAATCAGTGCCTGAAGGACCACCACAA
AACTGCGTAACAGGCAACATCACAGGAAAGTCCTTTTCAATTTTATGGGACCCACCAACTATAGTAACAGGG
AAATTTAGTTATAGAGTTGAATTATATGGACCATCAGGTCGCATTTTGGATAACAGCACAAAAGACCTCAAG
TTTGCATTCACTAACCTAACACCATTTACAATGTATGATGTCTATATTGCGGCTGAAACCAGTGCAGGGACT
GGGCCCAAGTCAAATATTTCAGTATTCACTCCACCAGATGTTCCAGGGGCAGTGTTTGATTTACAACTTGCA
GAGGTAGAATCCACGCAAGTAAGAATTACTTGGAAGAAACCACGACAACCAAATGGAATTATTAACCAATAC
CGAGTGAAAGTGCTAGTTCCAGAGACAGGAATAATTTTGGAAAATACTTTGCTCACTGGAAATAATGAGATA
AATGACCCCATGGCTCCAGAAATTGTGAACATAGTAGAGCCAATGGTAGGATTATATGAGGGTTCAGCAGAG
ATGTCGTCTGACCTTCACTCACTTGCTACATTTATATATAACAGCCATCCAGATAAAAACTTTCCTGCAAGG
AATAGAGCTGAAGACCAGACTTCACCAGTTGTAACTACAAGGAATCAGTATATTACTGACATTGCAGCTGAA
CAGCTGTCTTATGTTATCAGGAGACTTGTACCTTTCACTGAGCACATGATTAGTGTATCTGCTTTCACCATC
ATGGGAGAAGGACCACCAACAGTTCTCAGTGTTAGGACACGTCAGCAAGTGCCAAGCTCCATTAAAATTATA
AACTATAAAAATATTAGTTCTTCATCTATTTTGTTATATTGGGATCCTCCAGAATATCCCAATGGAAAAATA
ACTCACTATACGATTTATGCAATGGAATTGGATACAAACAGAGCATTCCAGATAACTACCATAGATAACAGC
TTTCTCATAACAGGTATAGGGTTAAAGAAATACACAAAATACAAAATGAGAGTGGCAGCCTCAACCCACGTT
GGAGAAAGTTCTTTGTCTGAAGAAAATGACATCTTTGTGAGAACTTCAGAAGATGAACCGGAATCATCACCT
CAAGATGTCGAAGTAATTGATGTTACCGCAGATGAAATAAGGTTGAAGTGGTCACCACCCGAAAAGCCCAAT
GGGATCATTATTGCTTATGAAGTGCTATATAAAAATATAGATACTTTATATATGAAGAACACATCAACAACA
GACATAATATTAAGGAACTTAAGACCTCACACCCTCTATAACATTTCTGTAAGGTCTTACACCAGATTTGGT
CATGGCAATCAGGTATCTTCTTTACTCTCTGTAAGGACTTCGGAGACTGTGCCTGATAGTGCACCAGAAAAT
ATCACTTACAAAAATATTTCTTCTGGAGAGATTGAGCTATCATTCCTTCCCCCAAGTAGTCCCAATGGAATC
ATACAAAAATATACAATTTATCTCAAGAGAAGTAATGGAAATGAGGAAAGAACTATAAATACAACCTCTTTA
ACCCAAAACATTCTGAAGAAATATACCCAATATATCATTGAGGTGTCTGCTAGTACACTCAAAGGTGAAGGA
GTTCGGAGTGCTCCCATAAGTATACTGACGGAGGAAGATGCTCCTGATTCTCCCCCTCAAGACTTCTCTGTA
AAACAGTTGTCTGGTGTCACGGTGAAGTTGTCATGGCAACCACCCCTGGAGCCAAATGGAATTATCCTTTAT
TACACAGTTTATGTCTGGAGGAATAGATCATCATTAAAAACTATTAATGTCACTGAAACATCATTGGAGTTA
TCAGATTTGGATTATAATGTTGAATACAGTGCTTATGTAACAGCTAGCACCAGATTTGGTGATGGGAAAACA
AGAAGCAATATCATTAGCTTTCAAACACCAGAGGGACCAAGCGATCCTCCCAAAGATGTTTATTATGCAAAC
CTCAGTTCTTCATCAATAATTCTTTTCTGGACACCTCCTTCAAAACCTAATGGGATTATACAATATTACTCT
GTTTATTACAGAAATACTTCAGGTACTTTTATGCAGAATTTTACACTCCATGAAGTAACCAATGACTTTGAC
AATATGACTGTATCCACAATTATAGATAAACTGACAATATTCAGCTACTATACATTTTGGTTAACAGCAAGT
ACTTCAGTTGGAAATGGGAATAAAAGCAGTGACATCATTGAAGTATACACAGATCAAGACGTCCCTGAAGGG
TTTGTTGGAAACCTGACTTACGAATCCATTTCGTCAACTGCAATAAATGTAAGCTGGGTCCCACCGGCTCAA
CCAAACGGTCTAGTCTTCTACTATGTTTCACTGATCTTACAGCAGACTCCTCGCCATGTGAGACCACCTCTT
GTTACATATGAGAGAAGCATATATTTTGATAATCTGGAAAAATACACTGATTATATATTAAAAATTACTCCA
TCAACAGAAAAGGGATTCTCTGATACCTATACTGCCCAGCTATACATCAAGACTGAAGAAGATGTCCCAGAA
ACTTCACCAATAATCAACACTTTTAAAAACCTTTCCTCTACCTCAGTTCTCTTATCATGGGATCCCCCAGTA
AAGCCAAATGGTGCAATAATAAGTTATGATTTAACTTTACAAGGACCAAATGAAAATTATTCTTTCATTACT
TCTGATAATTACATAATATTGGAAGAGCTTTCACCATTTACATTATATAGCTTTTTTGCTGCCGCAAGAACT
AGAAAAGGACTTGGTCCTTCCAGTATTCTTTTCTTTTACACAGATGAGTCAGTGCCGTTAGCACCTCCACAA
AATTTGACTTTAATCAACTGTACTTCAGACTTTGTATGGCTGAAATGGAGCCCAAGTCCTCTTCCAGGTGGT
ATTGTTAAAGTATATAGTTTTAAAATTCATGAACATGAAACTGACACTATATATTATAAGAATATATCAGGA
TTTAAAACTGAAGCCAAACTTGTTGGACTGGAACCAGTCAGCACCTACTCTATCCGTGTATCTGCGTTCACC
AAAGTTGGAAATGGCAATCAATTTAGTAATGTAGTAAAATTCACAACCCAAGAATCAGTTCCAGATGTCGTG
CAGAATATGCAGTGCATGGCAACTAGCTGGCAGTCAGTTTTAGTGAAATGGGATCCACCCAAAAAGGCAAAT
GGAATAATAACGCAGTATATGGTAACAGTTGAAAGGAATTCTACAAAAGTTTCTCCCCAAGATCACATGTAC
ACTTTCATAAAGCTTCTTGCCAATACCTCATATGTCTTTAAAGTAAGAGCTTCAACCTCAGCTGGTGAAGGT

GATGAAAGCACATGCCATGTCAGCACACTACCTGAAACAGTTCCCAGTGTTCCCACAAATATTGCTTTTTCT
GATGTTCAGTCAACTAGTGCAACATTGACATGGATAAGACCTGACACTATCCTTGGCTACTTTCAAAATTAC
AAAATTACCACTCAACTTCGTGCTCAAAAATGCAAAGAATGGGAATCCGAAGAATGTGTTGAATATCAAAAA
ATTCAATACCTCTATGAAGCTCACTTAACTGAAGAGACAGTATATGGATTAAAGAAATTTAGATGGTATAGA
TTCCAAGTGGCTGCCAGCACCAATGCTGGCTATGGCAATGCTTCAAACTGGATTTCTACAAAAACTCTGCCT
GGCCCTCCAGATGGTCCTCCTGAAAATGTTCATGTAGTAGCAACATCACCTTTTAGCATCAGCATAAGCTGG
AGTGAACCTGCTGTCATTACTGGACCAACATGTTATCTGATTGATGTCAAATCGGTAGATAATGATGAATTT
AATATATCCTTCATCAAGTCAAATGAAGAAAATAAAACCATAGAAATTAAAGATTTAGAAATATTCACAAGG
TATTCTGTAGTGATCACTGCATTTACTGGGAACATTAGTGCTGCATATGTAGAAGGGAAGTCAAGTGCTGAA
ATGATTGTTACTACTTTAGAATCAGCCCCAAAGGACCCACCTAACAACATGACATTTCAGAAGATACCAGAT
GAAGTTACAAAATTTCAATTAACGTCCCTTCCTCCTTCTCAACCTAATGGAAATATCCAAGTATATCAAGCT
CTGGTTTACCGAGAAGATGATCCTACTGCTGTCCAGATTCACAACCTCAGTATTATACAGAAAACCAACACA
TTCGTCATTGCAATGCTAGAAGGACTAAAAGGTGGACATACATACAATATCAGTGTTTACGCAGTCAATAGT
GCTGGTGCAGGTCCAAAGGTTCCGATGAGAATAACCATGGATATCAAAGCTCCAGCACGACCAAAAACCAAA
CCAACCCCTATTTATGATGCCACAGGAAAACTGCTTGTGACTTCAACAACAATTACAATCAGAATGCCAATA
TGTTACTACAGTGATGATCATGGACCAATAAAAAATGTACAAGTGCTTGTGACAGAAACAGGAGCTCAGCAT
GATGGAAATGTAACAAAGTGGTATGATGCATATTTTAATAAAGCAAGGCCATATTTTACAAATGAAGGCTTT
CCTAACCCTCCATGTACAGAAGGAAAGACAAAGTTTAGTGGCAATGAAGAAATCTACATCATAGGTGCTGAT
AATGCATGCATGATTCCTGGCAATGAAGACAAAATTTGCAATGGACCACTGAAACCAAAAAAGCAATACTTA
TTTAAATTTAGAGCTACAAATATTATGGGACAATTTACTGACTCTGATTATTCTGACCCTGTTAAGACTTTA
GGCGAAGGACTTTCAGAAAGAACCCTAGAGATCATTCTTTCCGTCACTTTGTGTATCCTTTCAATAATTCTC
CTTGGAACAGCTATTTTTGCATTTGCAAGAATTCGACAGAAGCAGAAAGAAGGTGGCACATACTCTCCTCAG
GATGCAGAAATTATTGACACTAAATTGAAGCTGGATCAGCTCATCACAGTGGCAGACCTGGAACTGAAGGAC
GAGAGATTAACGCGGTTACTTAGTTATAGAAAATCCATCAAGCCAATAAGCAAGAAATCCTTCCTGCAACAT
GTTGAAGAGCTTTGCACAAACAACAACCTAAAGTTTCAAGAAGAATTTTCGGAATTACCAAAATTTCTTCAG
GATCTTTCTTCAACTGATGCTGATCTGCCTTGGAATAGAGCAAAAAACCGCTTCCCAAACATAAAACCATAT
AATAATAACAGAGTAAAGCTGATAGCTGACGCTAGTGTTCCAGGTTCGGATTATATTAATGCCAGCTATATT
TCTGGTTATTTATGTCCAAATGAATTTATTGCTACTCAAGGTCCACTACCAGGAACAGTTGGAGATTTTTGG
AGAATGGTGTGGGAAACCAGAGCAAAAACATTAGTAATGCTAACACAGTGTTTTGAAAAAGGACGGATCAGA
TGCCATCAGTATTGGCCAGAGGACAACAAGCCAGTTACTGTCTTTGGAGATATAGTGATTACAAAGCTAATG
GAGGATGTTCAAATAGATTGGACTATCAGGGATCTGAAAATTGAAAGGCATGGGGATTGCATGACTGTTCGA
CAGTGTAACTTTACTGCCTGGCCAGAGCATGGGGTTCCTGAGAACAGCGCCCCTCTAATTCACTTTGTGAAG
TTGGTTCGAGCAAGCAGGGCACATGACACCACACCTATGATTGTTCACTGTAGTGCTGGAGTTGGAAGAACT
GGAGTTTTTATTGCTCTGGACCATTTAACACAACATATAAATGACCATGATTTTGTGGATATATATGGACTA
GTAGCTGAACTGAGAAGTGAAAGAATGTGCATGGTGCAGAATCTGGCACAGTATATCTTTTTACACCAGTGC
ATTCTGGATCTCTTATCAAATAAGGGAAGTAATCAGCCCATCTGTTTTGTTAACTATTCAGCACTTCAGAAG
ATGGACTCTTTGGACGCCATGGAAGGTGATGTTGAGCTTGAATGGGAAGAAACCACTATGTAA

In a search of public sequence databases, the NOV2c nucleic acid sequence, located on chromsome 12 has 5903 of 6906 bases (85%) identical to a gb:GENBANK-ID:AF063249|acc:AF063249.1 mRNA from *Rattus norvegicus* (*Rattus norvegicus* glomerular mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete cds) (E =0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV2c polypeptide (SEQ ID NO:10) encoded by SEQ ID NO:9 has 2300 amino acid residues and is presented in Table 2F using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV2c has a signal peptide and is likely to be localized in the plasma membrane with a certainty of 0.4600. In other embodiments, NOV2c may also be localized to the microbody (peroxisome) with acertainty of 0.1260, the endoplasmic reticulum (membrane) with a certainty of 0.1000 or in the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for a NOV2c peptide is between amino acids 17 and 18, at: SET-QV.

Table 2F. Encoded NOV2c protein sequence (SEQ ID NO:10).

```
MDFLIIFLLLFIGTSETQVDVSNVVPGTRYDITISSISTTYTSPVTRIVTTNVTEPGPPVFLAGERVGSAGI
LLSWNTPPNPNGRIISYIVKYKEVCPWMQTVYTQVRSKPDSLEVLLTNLNPGTTYEIKVAAENSAGIGVFSD
PFLFQTAESPAPGKVVNLTVEAYNASAVKLIWYLPRQPNGKITSFKISVKHARSGIVVKDVSIRVEDILTGK
LPECNVENSESFLWSTASPSPTLGRVTPPSRTTHSSSTLTQNEISSVWKEPISFVVTHLRPYTTYLFEVSAA
TTEAGYIDSTIVRTPESVPEGPPQNCVTGNITGKSFSILWDPPTIVTGKFSYRVELYGPSGRILDNSTKDLK
FAFTNLTPFTMYDVYIAAETSAGTGPKSNISVFTPPDVPGAVFDLQLAEVESTQVRITWKKPRQPNGIINQY
RVKVLVPETGIILENTLLTGNNEINDPMAPEIVNIVEPMVGLYEGSAEMSSDLHSLATFIYNSHPDKNFPAR
NRAEDQTSPVVTTRNQYITDIAAEQLSYVIRRLVPFTEHMISVSAFTIMGEGPPTVLSVRTRQQVPSSIKII
NYKNISSSSILLYWDPPEYPNGKITHYTIYAMELDTNRAFQITTIDNSFLITGIGLKKYTKYKMRVAASTHV
GESSLSEENDIFVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEKPNGIIIAYEVLYKNIDTLYMKNTSTT
DIILRNLRPHTLYNISVRSYTRFGHGNQVSSLLSVRTSETVPDSAPENITYKNISSGEIELSFLPPSSPNGI
IQKYTIYLKRSNGNEERTINTTSLTQNILKKYTQYIIEVSASTLKGEGVRSAPISILTEEDAPDSPPQDFSV
KQLSGVTVKLSWQPPLEPNGIILYYTVYVWRNRSSLKTINVTETSLELSDLDYNVEYSAYVTASTRFGDGKT
RSNIISFQTPEGPSDPPKDVYYANLSSSSIILFWTPPSKPNGIIQYYSVYYRNTSGTFMQNFTLHEVTNDFD
NMTVSTIIDKLTIFSYYTFWLTASTSVGNGNKSSDIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVPPAQ
PNGLVFYYVSLILQQTPRHVRPPLVTYERSIYFDNLEKYTDYILKITPSTEKGFSDTYTAQLYIKTEEDVPE
TSPIINTFKNLSSTSVLLSWDPPVKPNGAIISYDLTLQGPNENYSFITSDNYIILEELSPFTLYSFFAAART
RKGLGPSSILFFYTDESVPLAPPQNLTLINCTSDFVWLKWSPSPLPGGIVKVYSFKIHEHETDTIYYKNISG
FKTEAKLVGLEPVSTYSIRVSAFTKVGNGNQFSNVVKFTTQESVPDVVQNMQCMATSWQSVLVKWDPPKKAN
GIITQYMVTVERNSTKVSPQDHMYTFIKLLANTSYVFKVRASTSAGEGDESTCHVSTLPETVPSVPTNIAFS
DVQSTSATLTWIRPDTILGYFQNYKITTQLRAQKCKEWESEECVEYQKIQYLYEAHLTEETVYGLKKFRWYR
FQVAASTNAGYGNASNWISTKTLPGPPDGPPENVHVVATSPFSISISWSEPAVITGPTCYLIDVKSVDNDEF
NISFIKSNEENKTIEIKDLEIFTRYSVVITAFTGNISAAYVEGKSSAEMIVTTLESAPKDPPNNMTFQKIPD
EVTKFQLTSLPPSQPNGNIQVYQALVYREDDPTAVQIHNLSIIQKTNTFVIAMLEGLKGGHTYNISVYAVNS
AGAGPKVPMRITMDIKAPARPKTKPTPIYDATGKLLVTSTTITIRMPICYYSDDHGPIKNVQVLVTETGAQH
DGNVTKWYDAYFNKARPYFTNEGFPNPPCTEGKTKFSGNEEIYIIGADNACMIPGNEDKICNGPLKPKKQYL
FKFRATNIMGQFTDSDYSDPVKTLGEGLSERTLEIILSVTLCILSIILLGTAIFAFARIRQKQKEGGTYSPQ
DAEIIDTKLKLDQLITVADLELKDERLTRLLSYRKSIKPISKKSFLQHVEELCTNNNLKFQEEFSELPKFLQ
DLSSTDADLPWNRAKNRFPNIKPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGPLPGTVGDFW
RMVWETRAKTLVMLTQCFEKGRIRCHQYWPEDNKPVTVFGDIVITKLMEDVQIDWTIRDLKIERHGDCMTVR
QCNFTAWPEHGVPENSAPLIHFVKLVRASRAHDTTPMIVHCSAGVGRTGVFIALDHLTQHINDHDFVDIYGL
VAELRSERMCMVQNLAQYIFLHQCILDLLSNKGSNQPICFVNYSALQKMDSLDAMEGDVELEWEETTM
```

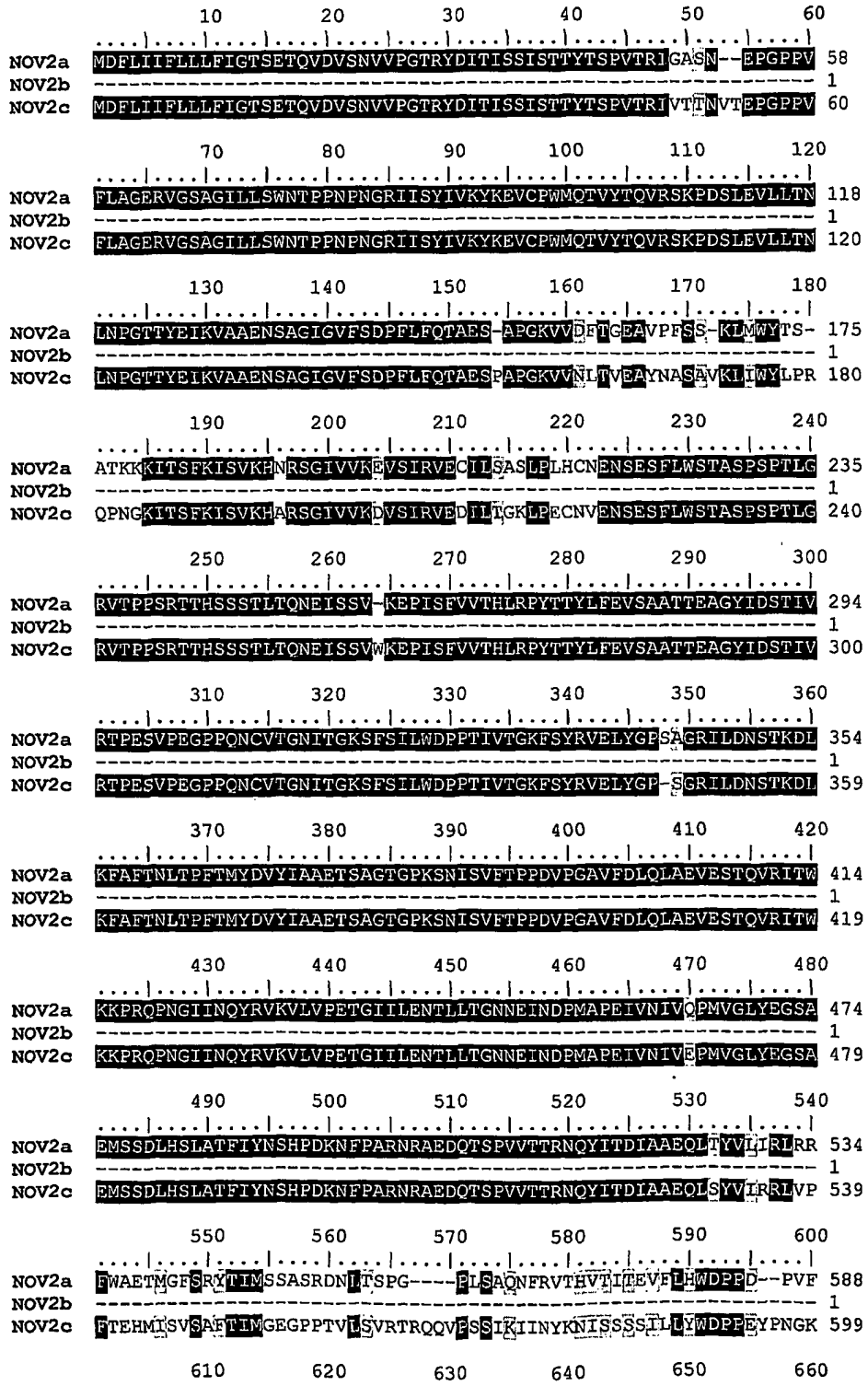
A search of sequence databases reveals that the NOV2c amino acid sequence has 1988 of 2301 amino acid residues (86%) identical to, and 2151 of 2301 amino acid residues (93%) similar to, the 2302 amino acid residue ptnr:SPTREMBL-ACC:O88488 protein from *Rattus norvegicus* (Rat) (Glomerular Mesangial Cell Receptor Protein-Tyrosine Phosphatase Precursor (EC 3.1.3.48)) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

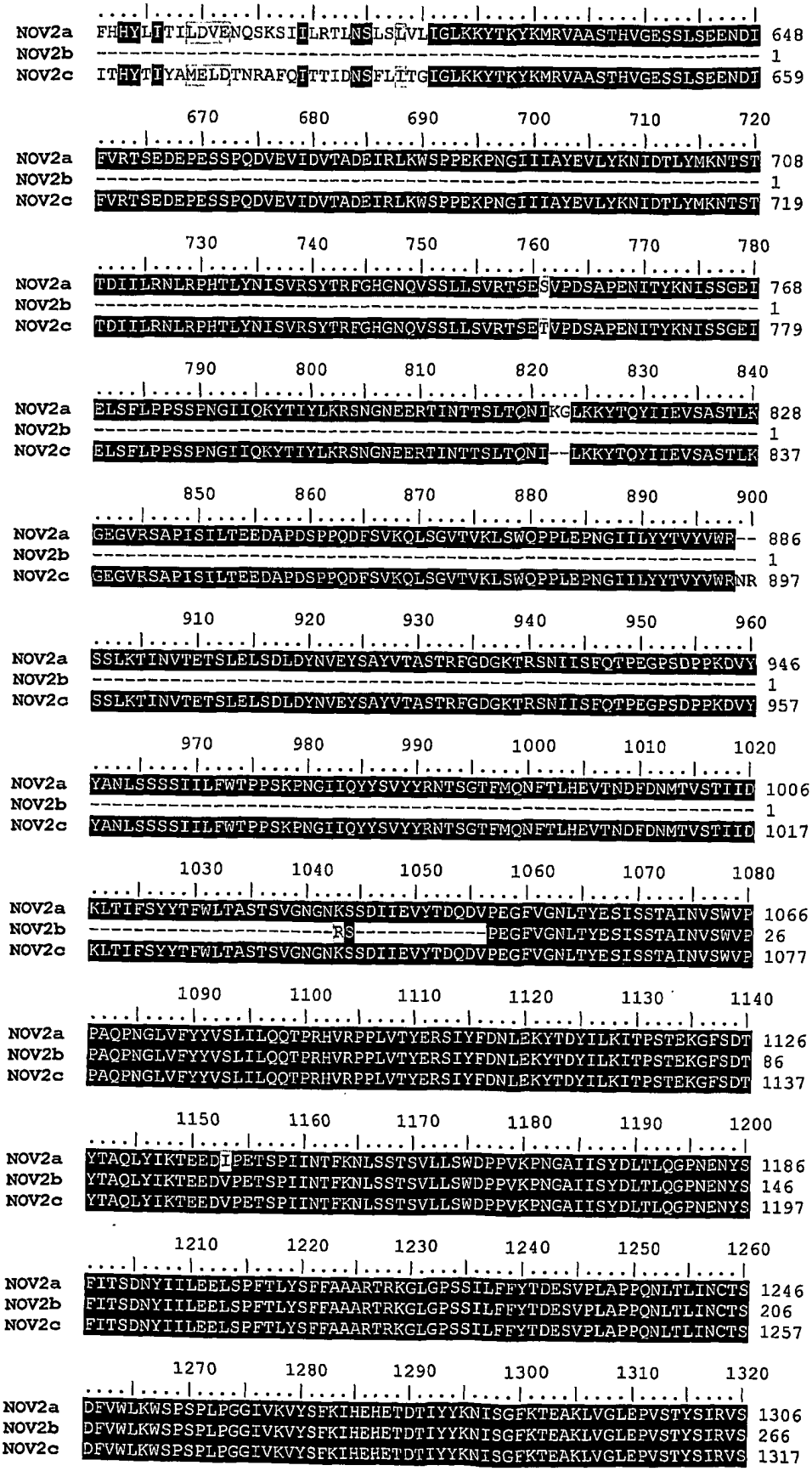
NOV2c is expressed in at least Synovium/Synovial membrane, Kidney. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG50718-05. The sequence is predicted to be expressed in the *Rattus norvegicus* :glomerular mesangial. because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF063249|acc:AF063249.1) a closely related *Rattus norvegicus* glomerular mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete cds homolog.

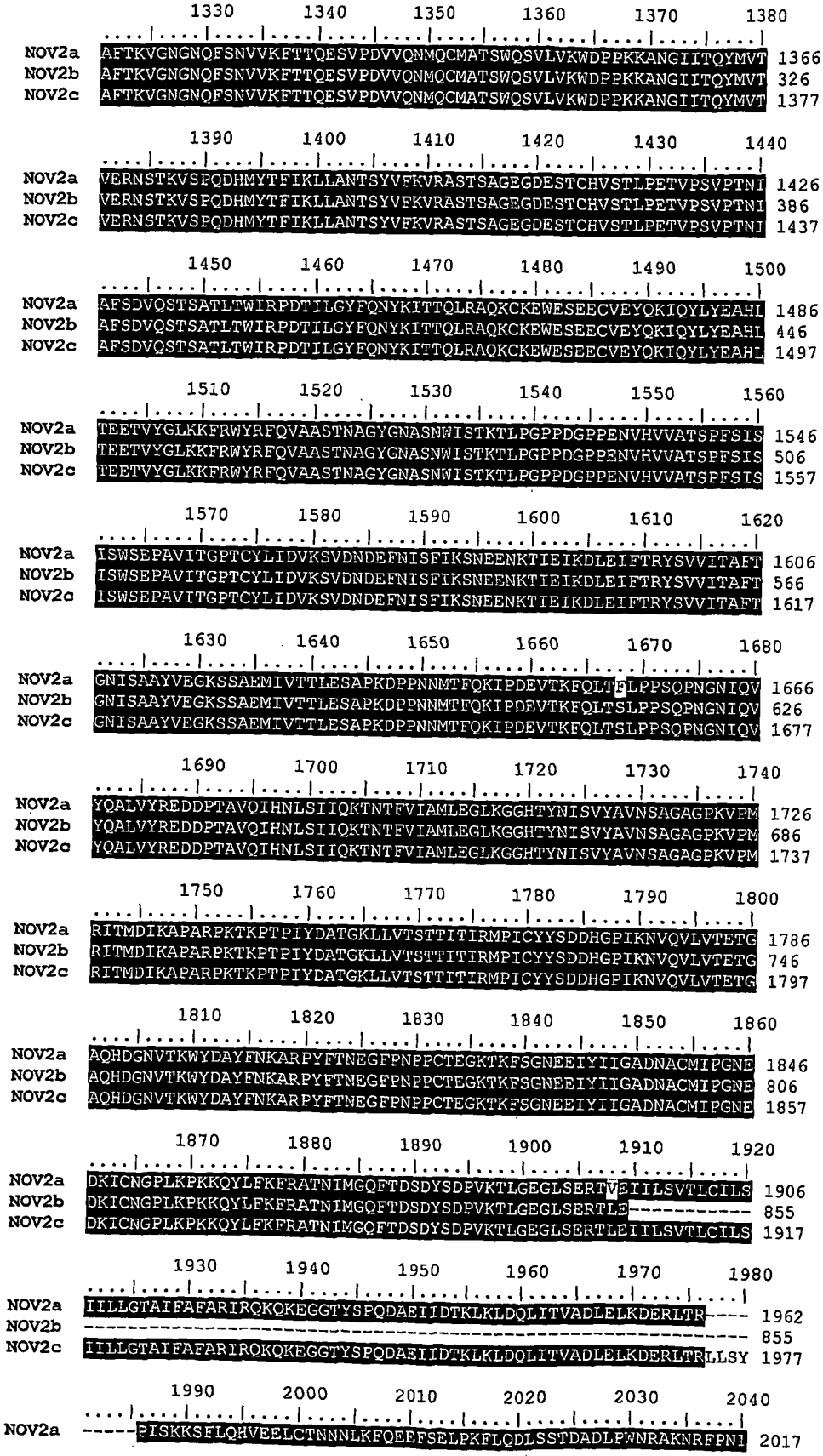
Homologies among each of the above NOV2 proteins will be shared by the other NOV2 proteins insofar as they are homologous to each other as shown below in Table 2G.

Any reference to NOV2 is assumed to refer to all three of the NOV2 proteins in general, unless otherwise noted.

Table 2G Alignment of NOV2a, b, and c




NOV2a FHHYLITILDVENQSKSILRTLNSLSLVLIGLKKYTKYKMRVAASTHVGESSLSEENDI 648
NOV2b ---------- 1
NOV2c ITHYTIYAMELDTNRAFQITTIDNSFLITGIGLKKYTKYKMRVAASTHVGESSLSEENDI 659
670 680 690 700 710 720
NOV2a FVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEKPNGIIIAYEVLYKNIDTLYMKNTST 708
NOV2b ---------- 1
NOV2c FVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEKPNGIIIAYEVLYKNIDTLYMKNTST 719
730 740 750 760 770 780
NOV2a TDIILRNLRPHTLYNISVRSYTRFGHGNQVSSLLSVRTSESVPDSAPENITYKNISSGEI 768
NOV2b ---------- 1
NOV2c TDIILRNLRPHTLYNISVRSYTRFGHGNQVSSLLSVRTSETVPDSAPENITYKNISSGEI 779
790 800 810 820 830 840
NOV2a ELSFLPPSSPNGIIQKYTIYLKRSNGNEERTINTTSLTQNIKGLKKYTQYIIEVSASTLK 828
NOV2b ---------- 1
NOV2c ELSFLPPSSPNGIIQKYTIYLKRSNGNEERTINTTSLTQNI--LKKYTQYIIEVSASTLK 837
850 860 870 880 890 900
NOV2a GEGVRSAPISILTEEDAPDSPPQDFSVKQLSGVTVKLSWQPPLEPNGIILYYTVYVWR-- 886
NOV2b ---------- 1
NOV2c GEGVRSAPISILTEEDAPDSPPQDFSVKQLSGVTVKLSWQPPLEPNGIILYYTVYVWRNR 897
910 920 930 940 950 960
NOV2a SSLKTINVTETSLELSDLDYNVEYSAYVTASTRFGDGKTRSNIISFQTPEGPSDPPKDVY 946
NOV2b ---------- 1
NOV2c SSLKTINVTETSLELSDLDYNVEYSAYVTASTRFGDGKTRSNIISFQTPEGPSDPPKDVY 957
970 980 990 1000 1010 1020
NOV2a YANLSSSSIILFWTPPSKPNGIIQYYSVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIID 1006
NOV2b ---------- 1
NOV2c YANLSSSSIILFWTPPSKPNGIIQYYSVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIID 1017
1030 1040 1050 1060 1070 1080
NOV2a KLTIFSYYTFWLTASTSVGNGNKSSDIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVP 1066
NOV2b ----------RS----------PEGFVGNLTYESISSTAINVSWVP 26
NOV2c KLTIFSYYTFWLTASTSVGNGNKSSDIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVP 1077
1090 1100 1110 1120 1130 1140
NOV2a PAQPNGLVFYYVSLILQQTPRHVRPPLVTYERSIYFDNLEKYTDYILKITPSTEKGFSDT 1126
NOV2b PAQPNGLVFYYVSLILQQTPRHVRPPLVTYERSIYFDNLEKYTDYILKITPSTEKGFSDT 86
NOV2c PAQPNGLVFYYVSLILQQTPRHVRPPLVTYERSIYFDNLEKYTDYILKITPSTEKGFSDT 1137
1150 1160 1170 1180 1190 1200
NOV2a YTAQLYIKTEEDIPETSPIINTFKNLSSTSVLLSWDPPVKPNGAIISYDLTLQGPNENYS 1186
NOV2b YTAQLYIKTEEDVPETSPIINTFKNLSSTSVLLSWDPPVKPNGAIISYDLTLQGPNENYS 146
NOV2c YTAQLYIKTEEDVPETSPIINTFKNLSSTSVLLSWDPPVKPNGAIISYDLTLQGPNENYS 1197
1210 1220 1230 1240 1250 1260
NOV2a FITSDNYIILEELSPFTLYSFFAAARTRKGLGPSSILFFYTDESVPLAPPQNLTLINCTS 1246
NOV2b FITSDNYIILEELSPFTLYSFFAAARTRKGLGPSSILFFYTDESVPLAPPQNLTLINCTS 206
NOV2c FITSDNYIILEELSPFTLYSFFAAARTRKGLGPSSILFFYTDESVPLAPPQNLTLINCTS 1257
1270 1280 1290 1300 1310 1320
NOV2a DFVWLKWSPSPLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVGLEPVSTYSIRVS 1306
NOV2b DFVWLKWSPSPLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVGLEPVSTYSIRVS 266
NOV2c DFVWLKWSPSPLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVGLEPVSTYSIRVS 1317


1330 1340 1350 1360 1370 1380
NOV2a AFTKVGNGNQFSNVVKFTTQESVPDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMVT 1366
NOV2b AFTKVGNGNQFSNVVKFTTQESVPDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMVT 326
NOV2c AFTKVGNGNQFSNVVKFTTQESVPDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMVT 1377
1390 1400 1410 1420 1430 1440
NOV2a VERNSTKVSPQDHMYTFIKLLANTSYVFKVRASTSAGEGDESTCHVSTLPETVPSVPTNI 1426
NOV2b VERNSTKVSPQDHMYTFIKLLANTSYVFKVRASTSAGEGDESTCHVSTLPETVPSVPTNI 386
NOV2c VERNSTKVSPQDHMYTFIKLLANTSYVFKVRASTSAGEGDESTCHVSTLPETVPSVPTNI 1437
1450 1460 1470 1480 1490 1500
NOV2a AFSDVQSTSATLTWIRPDTILGYFQNYKITTQLRAQKCKEWESEECVEYQKIQYLYEAHL 1486
NOV2b AFSDVQSTSATLTWIRPDTILGYFQNYKITTQLRAQKCKEWESEECVEYQKIQYLYEAHL 446
NOV2c AFSDVQSTSATLTWIRPDTILGYFQNYKITTQLRAQKCKEWESEECVEYQKIQYLYEAHL 1497
1510 1520 1530 1540 1550 1560
NOV2a TEETVYGLKKFRWYRFQVAASTNAGYGNASNWISTKTLPGPPDGPPENVHVVATSPFSIS 1546
NOV2b TEETVYGLKKFRWYRFQVAASTNAGYGNASNWISTKTLPGPPDGPPENVHVVATSPFSIS 506
NOV2c TEETVYGLKKFRWYRFQVAASTNAGYGNASNWISTKTLPGPPDGPPENVHVVATSPFSIS 1557
1570 1580 1590 1600 1610 1620
NOV2a ISWSEPAVITGPTCYLIDVKSVDNDEFNISFIKSNEENKTIEIKDLEIFTRYSVVITAFT 1606
NOV2b ISWSEPAVITGPTCYLIDVKSVDNDEFNISFIKSNEENKTIEIKDLEIFTRYSVVITAFT 566
NOV2c ISWSEPAVITGPTCYLIDVKSVDNDEFNISFIKSNEENKTIEIKDLEIFTRYSVVITAFT 1617
1630 1640 1650 1660 1670 1680
NOV2a GNISAAYVEGKSSAEMIVTTLESAPKDPPNNMTFQKIPDEVTKFQLTFLPPSQPNGNIQV 1666
NOV2b GNISAAYVEGKSSAEMIVTTLESAPKDPPNNMTFQKIPDEVTKFQLTSLPPSQPNGNIQV 626
NOV2c GNISAAYVEGKSSAEMIVTTLESAPKDPPNNMTFQKIPDEVTKFQLTSLPPSQPNGNIQV 1677
1690 1700 1710 1720 1730 1740
NOV2a YQALVYREDDPTAVQIHNLSIIQKTNTFVIAMLEGLKGGHTYNISVYAVNSAGAGPKVPM 1726
NOV2b YQALVYREDDPTAVQIHNLSIIQKTNTFVIAMLEGLKGGHTYNISVYAVNSAGAGPKVPM 686
NOV2c YQALVYREDDPTAVQIHNLSIIQKTNTFVIAMLEGLKGGHTYNISVYAVNSAGAGPKVPM 1737
1750 1760 1770 1780 1790 1800
NOV2a RITMDIKAPARPKTKPTPIYDATGKLLVTSTTITIRMPICYYSDDHGPIKNVQVLVTETG 1786
NOV2b RITMDIKAPARPKTKPTPIYDATGKLLVTSTTITIRMPICYYSDDHGPIKNVQVLVTETG 746
NOV2c RITMDIKAPARPKTKPTPIYDATGKLLVTSTTITIRMPICYYSDDHGPIKNVQVLVTETG 1797
1810 1820 1830 1840 1850 1860
NOV2a AQHDGNVTKWYDAYFNKARPYFTNEGFPNPPCTEGKTKFSGNEEIYIIGADNACMIPGNE 1846
NOV2b AQHDGNVTKWYDAYFNKARPYFTNEGFPNPPCTEGKTKFSGNEEIYIIGADNACMIPGNE 806
NOV2c AQHDGNVTKWYDAYFNKARPYFTNEGFPNPPCTEGKTKFSGNEEIYIIGADNACMIPGNE 1857
1870 1880 1890 1900 1910 1920
NOV2a DKICNGPLKPKKQYLFKFRATNIMGQFTDSDYSDPVKTLGEGLSERTVEIILSVTLCILS 1906
NOV2b DKICNGPLKPKKQYLFKFRATNIMGQFTDSDYSDPVKTLGEGLSERTLE---------- 855
NOV2c DKICNGPLKPKKQYLFKFRATNIMGQFTDSDYSDPVKTLGEGLSERTLEIILSVTLCILS 1917
1930 1940 1950 1960 1970 1980
NOV2a IILLGTAIFAFARIRQKQKEGGTYSPQDAEIIDTKLKLDQLITVADLELKDERLTR---- 1962
NOV2b ---------- 855
NOV2c IILLGTAIFAFARIRQKQKEGGTYSPQDAEIIDTKLKLDQLITVADLELKDERLTRLLSY 1977
1990 2000 2010 2020 2030 2040
NOV2a -----PISKKSFLQHVEELCTNNNLKFQEEFSELPKFLQDLSSTDADLPWNRAKNRFPNI 2017

```
NOV2b  ------------------------------------------------------------ 855
NOV2c  RKSIKPISKKSFLQHVEELCTNNNLKFQEEFSELPKFLQDLSSTDADLPWNRAKNRFPNI 2037

                2050       2060       2070       2080       2090       2100
       ....|....|....|....|....|....|....|....|....|....|....|....|
NOV2a  KPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGPLPGTVGDFWRMVWETRAK 2077
NOV2b  ------------------------------------------------------------ 855
NOV2c  KPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGPLPGTVGDFWRMVWETRAK 2097

                2110       2120       2130       2140       2150       2160
       ....|....|....|....|....|....|....|....|....|....|....|....|
NOV2a  TLVMLTQCFEKGRIRCHQYWPEDNKPVTVFGDIVITKLMEDVQIDWTIRDLKIERHGDCM 2137
NOV2b  ------------------------------------------------------------ 855
NOV2c  TLVMLTQCFEKGRIRCHQYWPEDNKPVTVFGDIVITKLMEDVQIDWTIRDLKIERHGDCM 2157

                2170       2180       2190       2200       2210       2220
       ....|....|....|....|....|....|....|....|....|....|....|....|
NOV2a  TVRQCNFTAWPEHGVPENSAPLIHFVKLVRASRAHDTTPMIVHCSAGVGRTGVFIALDHL 2197
NOV2b  ------------------------------------------------------------ 855
NOV2c  TVRQCNFTAWPEHGVPENSAPLIHFVKLVRASRAHDTTPMIVHCSAGVGRTGVFIALDHL 2217

                2230       2240       2250       2260       2270       2280
       ....|....|....|....|....|....|....|....|....|....|....|....|
NOV2a  TQHINDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILDLLSNKGSNQPICFVNYSA 2257
NOV2b  ------------------------------------------------------------ 855
NOV2c  TQHINDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILDLLSNKGSNQPICFVNYSA 2277

                2290       2300
       ....|....|....|....|....
NOV2a  LQKMDSLDAMEGGDVELEWEETTM 2281 (SEQ ID NO:6)
NOV2b  ------------------------ 855  (SEQ ID NO:8)
NOV2c  LQKMDSLDAMEG-DVELEWEETTM 2300 (SEQ ID NO:10)
```

The disclosed NOV2a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 2H.

Table 2H. BLAST results for NOV2a

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|12621078|ref|NP_075214.1| (NM_022925)	protein tyrosine phosphatase, receptor type, Q [Rattus norvegicus]	2302	1893/2306 (82%)	2077/2306 (89%)	0.0
gi|125977|sp|P16621|LAR_DROME	PROTEIN-TYROSINE PHOSPHATASE DLAR PRECURSOR (PROTEIN-TYROSINE-PHOSPHATE PHOSPHOHYDROLASE)	2029	410/1587 (25%)	680/1587 (42%)	1e-94
gi|10728878|gb|AAF53837.2| (AE003663)	Lar gene product [Drosophila melanogaster]	2037	410/1587 (25%)	680/1587 (42%)	2e-94
gi|7290546|gb|AAF45998.1| (AE003432)	Ptp4E gene product [Drosophila melanogaster]	1767	417/1645 (25%)	694/1645 (41%)	8e-94

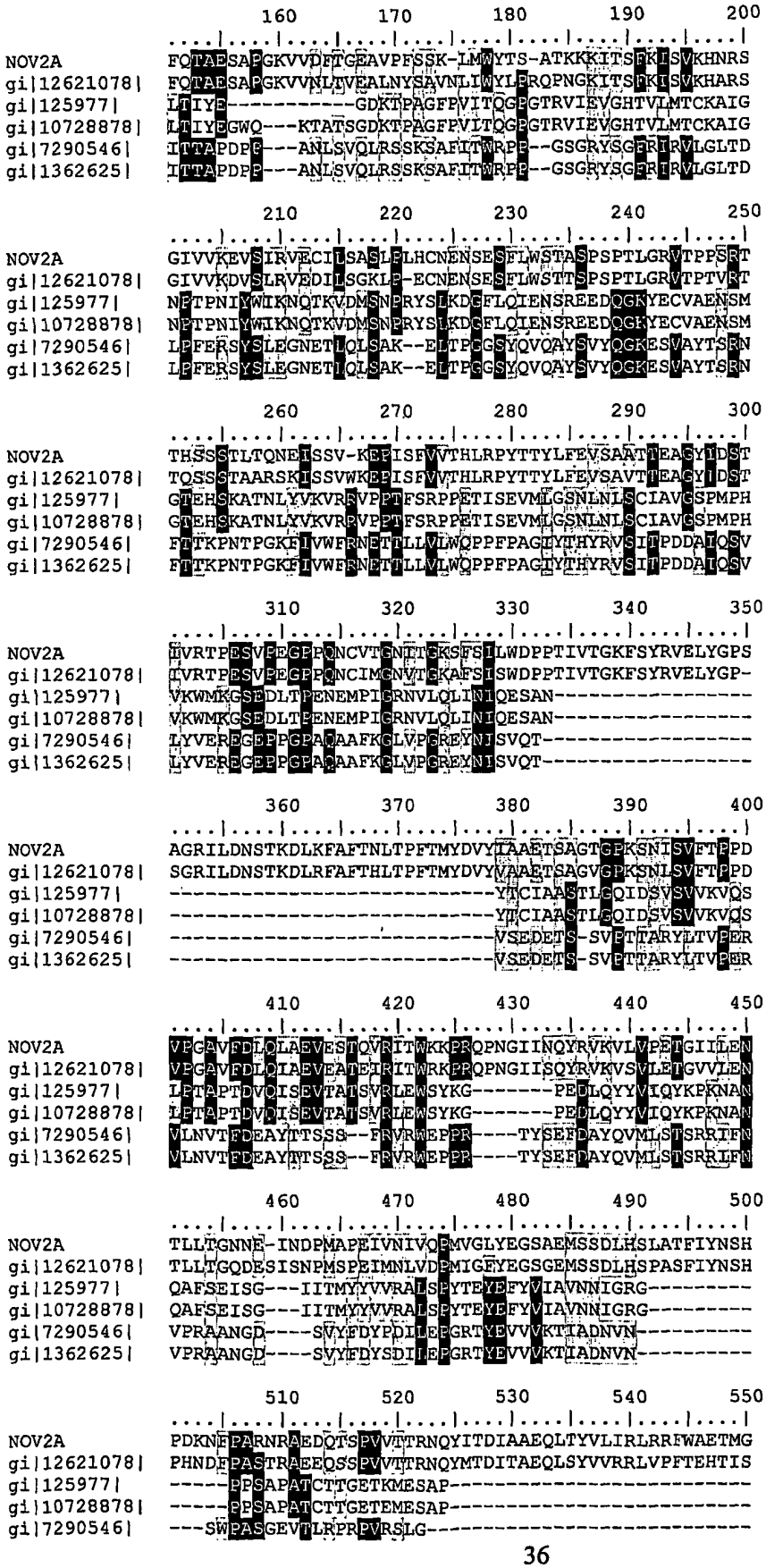
gi|1362625|pir||A49 502	protein-tyrosine-phosphatase (EC 3.1.3.48), receptor type 4E, splice form A precursor - fruit fly (Drosophila melanogaster)	1767	416/1645 (25%)	693/1645 (41%)	1e-92

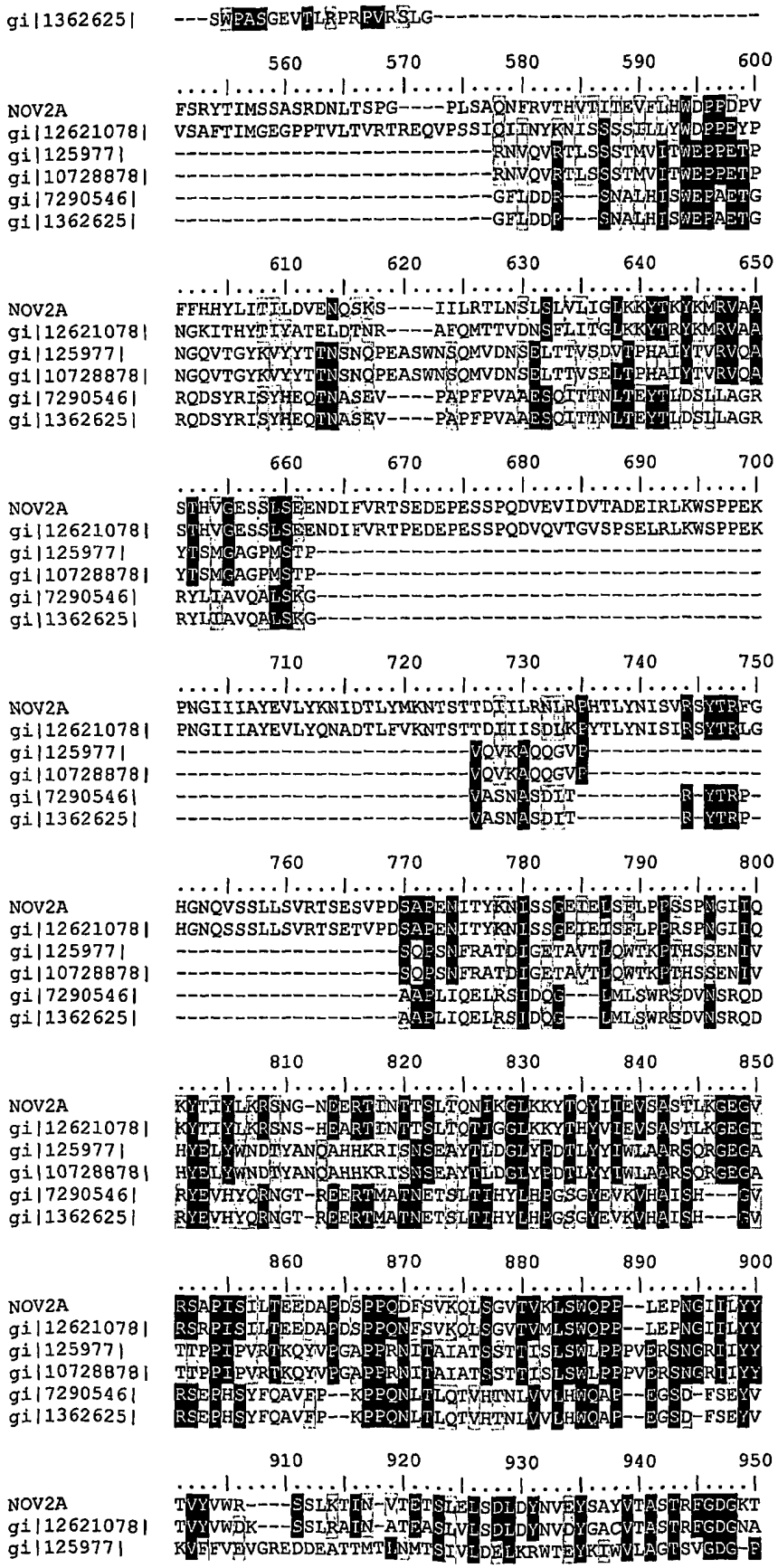
The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 2I. In the ClustalW alignment of the NOV2 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

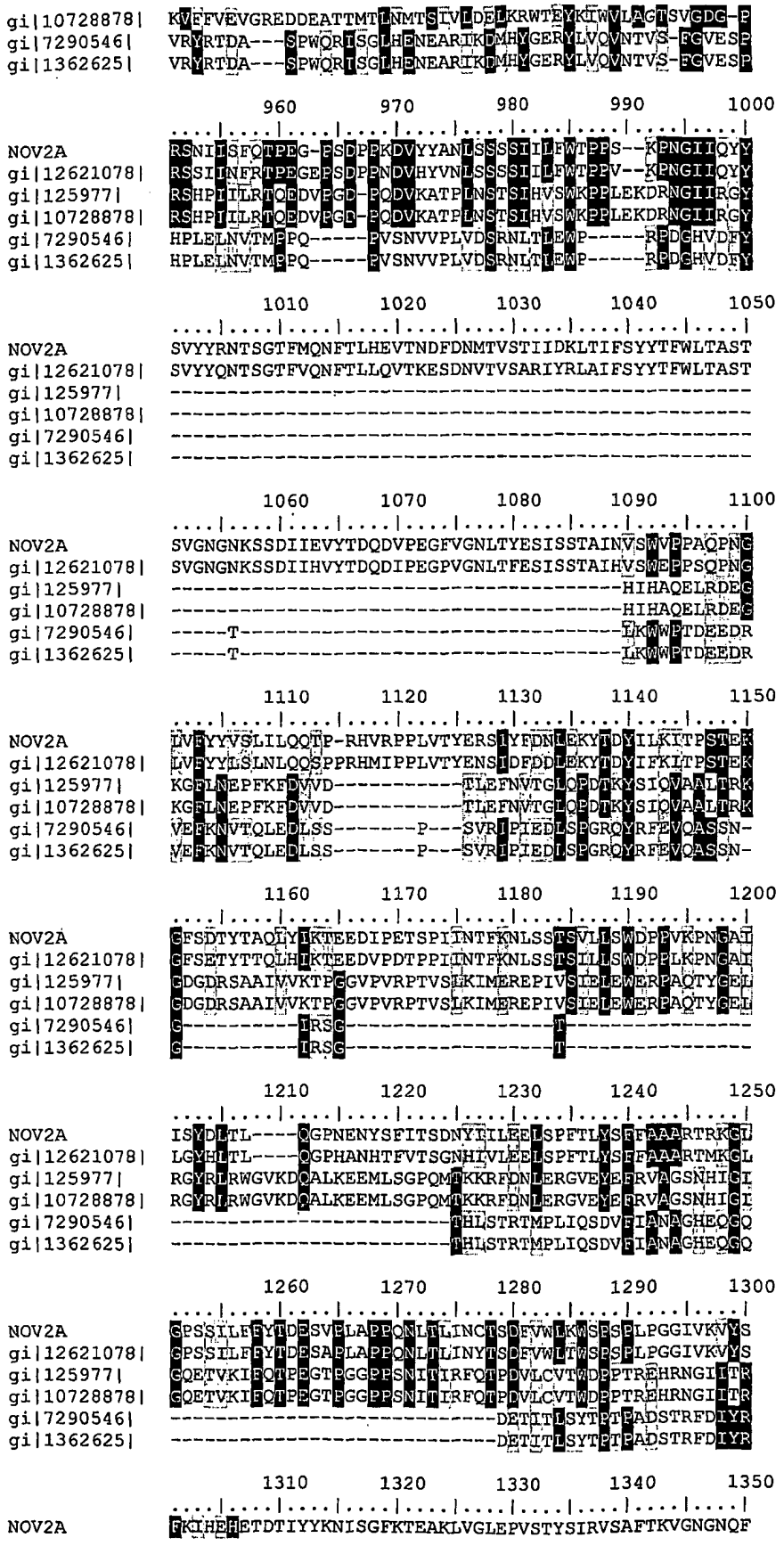
Table 2I. ClustalW Analysis of NOV2

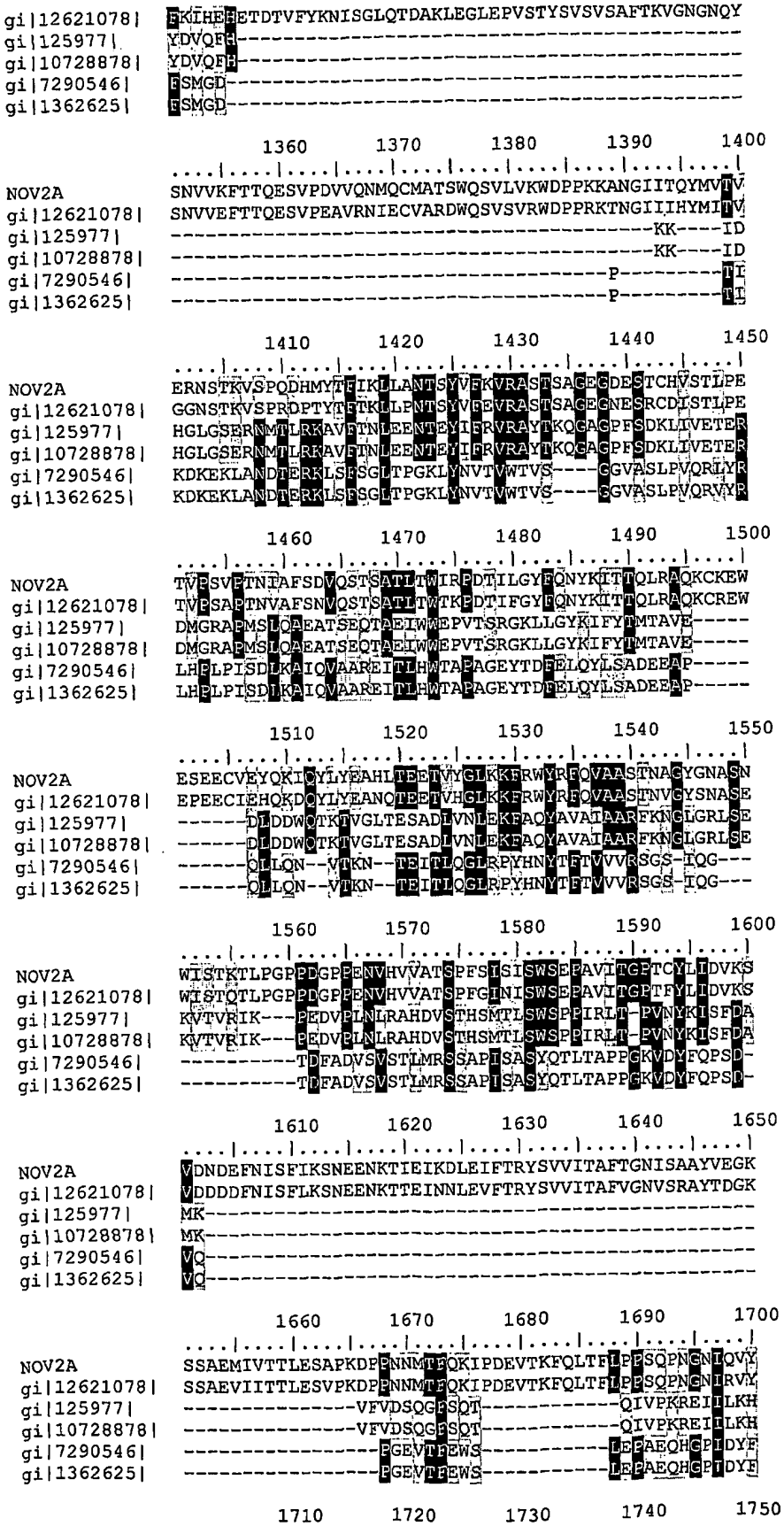
1) Novel NOV2a (SEQ ID NO:6)
2) gi|12621078|ref|NP_075214.1| (NM_022925) protein tyrosine phosphatase, receptor type, Q [Rattus norvegicus] (SEQ ID NO:37)
3) gi|125977|sp|P16621|LAR_DROME PROTEIN-TYROSINE PHOSPHATASE DLAR PRECURSOR (PROTEIN-TYROSINE-PHOSPHATE PHOSPHOHYDROLASE) (SEQ ID NO:38)
4) gi|10728878|gb|AAF53837.2| (AE003663) Lar gene product [Drosophila melanogaster] (SEQ ID NO:39)
5) gi|7290546|gb|AAF45998.1| (AE003432) Ptp4E gene product [Drosophila melanogaster] (SEQ ID NO:40)
6) gi|1362625|pir||A49502 protein-tyrosine-phosphatase (EC 3.1.3.48), receptor type 4E, splice form A precursor - fruit fly (Drosophila melanogaster) (SEQ ID NO:41)

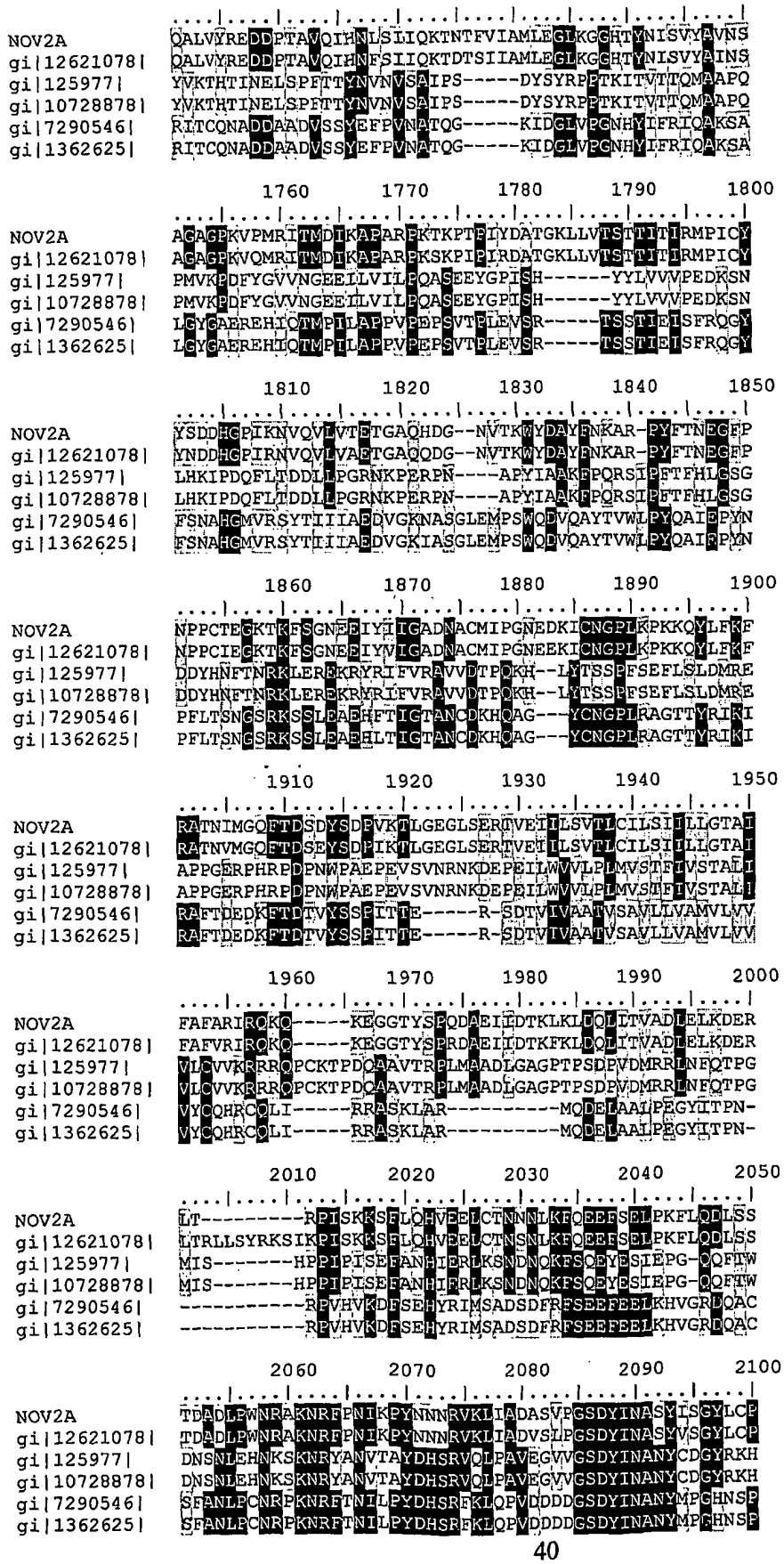
```
                        10        20        30        40        50
                ....|....|....|....|....|....|....|....|....|....|
NOV2A           -MDFLIIFLLLFIGTSETQVDVSNVVPGTRYDLTISSIS--TTYTSPVTR
gi|12621078|    MMDFHFSFLFLLIGTSESQVDVSSSFDGTGYDITLSSVSA-TTYSSPVSR
gi|125977|      ----------MGLQMTAARPIAALSLLVLSLLTWTHPTIVDAAHPPEIIRK
gi|10728878|    ----------MGLQMTAARPIAALSLLVLSLLTWTHPTIVDAAHPPEIIRK
gi|7290546|     -MDCATRKQQQLRAHHQQQQIQIQTHGRKRQQLQKQRHNHHHYYQNSQQQ
gi|1362625|     -MDCATRKQQQLRAHHQQQQIQIQTHGRKRQQLQKQRHNHHHYYQNPQQQ

                        60        70        80        90       100
                ....|....|....|....|....|....|....|....|....|....|
NOV2A           IGAS--NEPGPPVPLAGERVGSAGILLSWNTPPNPNGRIISYIVKYKEVC
gi|12621078|    TLATNVTKPGPPVPLAGERVGSAGILLSWNTPPNPNGRIISYVVKYKEVC
gi|125977|      PQNQGVRVGGVASFYCAARGDPPPSIVWRKNGKKVSG------------
gi|10728878|    PQNQGVRVGGVASFYCAARGDPPPSIVWRKNGKKVSG------------
gi|7290546|     QKHFVWLVVGILTIFLAQHANAADLVI--NVPNASSNANAFYRIDYSPPF
gi|1362625|     QKHFVWLVVGILTIFLARHANAADLVI--NVPNASSNANAFYRIDYSPPF

                       110       120       130       140       150
                ....|....|....|....|....|....|....|....|....|....|
NOV2A           PWMQTVYTQVRSKPDSLEVLLTNLNPGTTYEIKVAAENSAGIGVFSDPFL
gi|12621078|    PWMQTAYTRARAKPDSLEVLLTNLNPGTTYEIKVAAENNAGIGVFSDPFL
gi|125977|      -T-QSRYTVLEQPGGISILRIEPVRAGRDDAPYECVAENGVGDAVSADAT
gi|10728878|    -T-QSRYTVLEQPGGISILRIEPVRAGRDDAPYECVAENGVGDAVSADAT
gi|7290546|     GFPEPNTTIPASDIG-KDIKFSRALPGTEYNFWLYYTNSTHREQLTWTVN
gi|1362625|     GEPEPNTTIPASDIG-KDIKFSRALPGTEYNFWLYYTNSTHREQLTWTVN
```

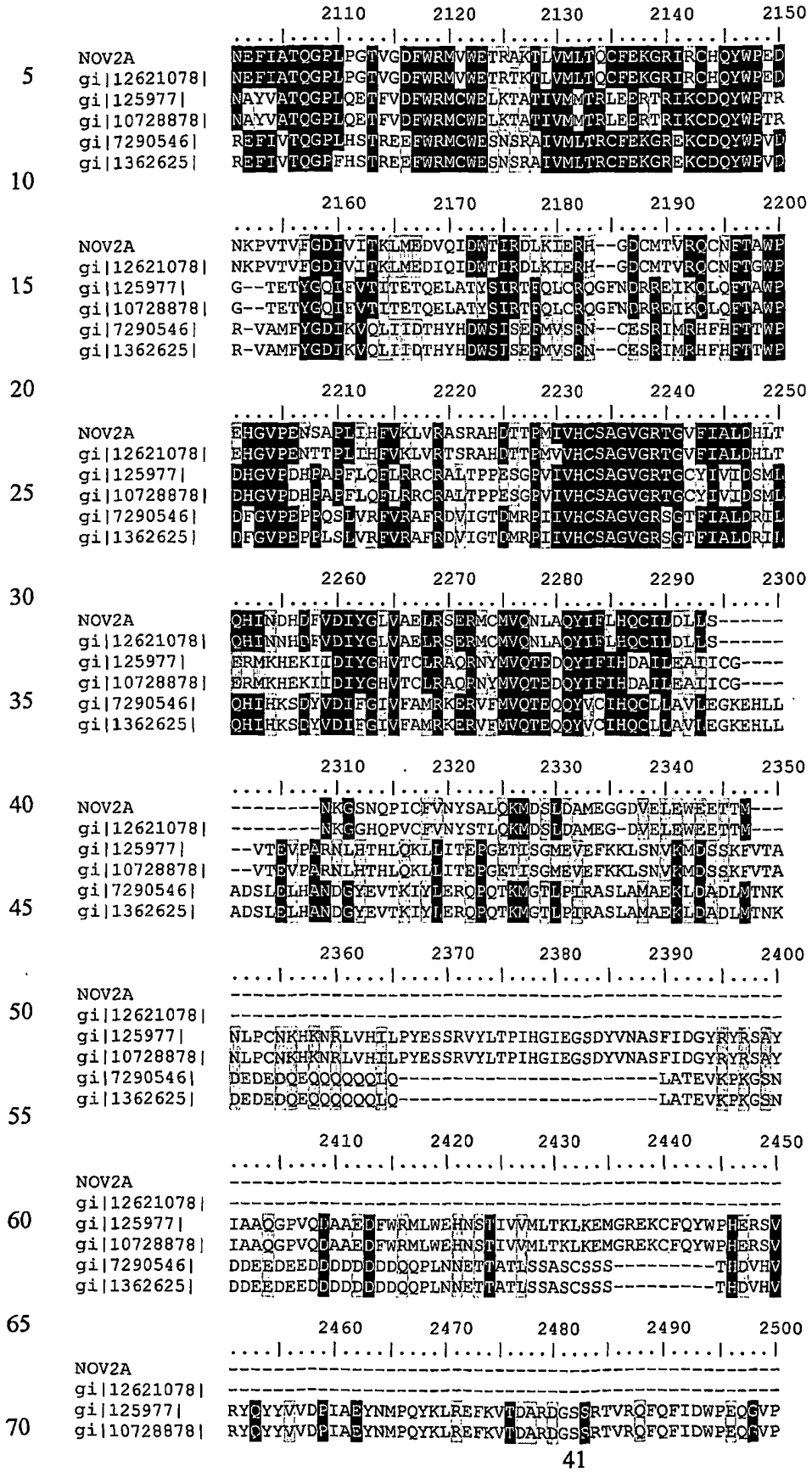

160 170 180 190 200
NOV2A FQTAESAPGKVVDFTGEAVPFSSK-LMWYTS-ATKKKITSFKISVKHNRS
gi|12621078| FQTAESAPGKVVNLTVEALNYSAVNLIWYLERQPNGKITSTKISVKHARS
gi|125977| LTIYE----------GDKTPAGFPVITQGPGTRVIEVGHTVLMTCKAIG
gi|10728878| LTIYPGWQ---KTATSGDKTPAGFPVITQGPGTRVIEVGHTVLMTCKAIG
gi|7290546| ITTAPDPG---ANLSVQLRSSKSAFITWRPE--GSGRYSGFRTRVLGLTD
gi|1362625| ITTAPDPP---ANLSVQLRSSKSAFITWRPP--GSGRYSGFRTRVLGLTD
210 220 230 240 250
NOV2A GIVVKEVSIRVECILSASLFLHCNENSESFLWSTASPSPTLGRVTPPSRT
gi|12621078| GIVVKDVSLRVEDILSGKLPECNENSESFLWSTTSPSPTLGRVTPTVPT
gi|125977| NFTPNIYWIKNQTKVDMSNPRYSLKDGFLQIENSREEDQGKYECVAENSM
gi|10728878| NFTPNIYWIKNQTKVDMSNPRYSLKDGFLQIENSREEDQGKYECVAENSM
gi|7290546| LPFERSYSLEGNETLQLSAK--ELTPGGSYQVQAYSVYQGKESVAYTSRN
gi|1362625| LPFERSYSLEGNETLQLSAK--ELTPGGSYQVQAYSVYQGKESVAYTSRN
260 270 280 290 300
NOV2A THSSSTLTQNEISSV-KEPISFVVTHLRPYTTYLFEVSAATTEAGYIDST
gi|12621078| TQSSSTAARSKISSVWKEPISFVVTHLRPYTTYLFEVSAVTTEAGYIDST
gi|125977| GTEHSKATNLYVKVRSVPPTFSRPPETISEVMLGSNLNLSCIAVGSPMPH
gi|10728878| GTEHSKATNLYVKVRPVPPTFSRPPETISEVMLGSNLNLSCIAVGSPMPH
gi|7290546| FTTKPNTPGKFIVWFRNETTLLVLWQPPFPAGIYTHYRVSITPDDAIQSV
gi|1362625| FTTKPNTPGKFIVWFRNETTLLVLWQPPFPAGIYTHYRVSITPDDAIQSV
310 320 330 340 350
NOV2A IVRTPESVPEGPPQNCVTGNTTGKSFSILWDPPTIVTGKFSYRVELYGPS
gi|12621078| IVRTPESVPEGPPQNCIMGNVTGKAFSISWDPPTIVTGKFSYRVELYGP-
gi|125977| VKWMKGSEDLTPENEMPIGRNVLQLINIQESAN----------
gi|10728878| VKWMKGSEDLTPENEMPIGRNVLQLINIQESAN----------
gi|7290546| LYVERPGEPPGPAQAAFKGLVPGREYNISVQT----------
gi|1362625| LYVERPGEPPGPAQAAFKGLVPGREYNISVQT----------
360 370 380 390 400
NOV2A AGRILDNSTKDLKFAFTNLTPFTMYDVYIAAETSAGTGPKSNISVFTPPD
gi|12621078| SGRILDNSTKDLRFAFTHLTPFTMYDVYVAAETSAGVGPKSNLSVFTPPD
gi|125977| ----------YTCIAASTLGQIDSVSVVKVQS
gi|10728878| ----------YTCIAASTLGQIDSVSVVKVQS
gi|7290546| ----------VSEDETS-SVPTTARYLTVPER
gi|1362625| ----------VSEDETS-SVPTTARYLTVPER
410 420 430 440 450
NOV2A VPGAVFDLQLAEVESTQVRITWKKPRQPNGIINQYRVKVLVPETGIILEN
gi|12621078| VPGAVFDLQIAEVEATEIRITWRKPPQPNGIISQYRVKVSVLETGVVLEN
gi|125977| LPTAPTDVQISEVTATSVRLEWSYKG--------PELLQYYVIQYKPKNAN
gi|10728878| LPTAPTDVQISEVTATSVRLEWSYKG--------PELLQYYVIQYKPKNAN
gi|7290546| VLNVTFDEAYTTSSS--FEVRWEPPR----TYSEFDAYQVMLSTSRRIFN
gi|1362625| VLNVTFDEAYTTSSS--FEVRWEPPP----TYSEFDAYQVMLSTSRRIFN
460 470 480 490 500
NOV2A TLLTGNNE-INDPMAPEIVNIVQPMVGLYEGSAEMSSDLHSLATFIYNSH
gi|12621078| TLLTGQDESISNPMSPEIMNLVDPMIGFYEGSGEMSSDLHSPASFIYNSH
gi|125977| QAFSEISG---IITMYYVVRALSPYTEYEFYVIAVNNIGRG---------
gi|10728878| QAFSEISG---IITMYYVVRALSPYTEYEFYVIAVNNIGRG---------
gi|7290546| VPRAANGD----SVYFDYPDILEPGRTYEVVVKTIADNVN----------
gi|1362625| VPRAANGD----SVYFDYSDILEPGRTYEVVVKTIADNVN----------
510 520 530 540 550
NOV2A PDKNEPARNRAEDQTSPVVTTRNQYITDIAAEQLTYVLIRLRRFWAETMG
gi|12621078| PHNDEPASTRAEEQSSPVVTTRNQYMTDITAEQLSYVVRRLVPFTEHTIS
gi|125977| -----EPSAPATCTTGETKMESAP----------
gi|10728878| -----EPSAPATCTTGETEMESAP----------
gi|7290546| ---SWPASGEVTLRPRPVRSLG----------


gi|1362625| ---SWPASGEVTLRPRPVRSLG----------
560 570 580 590 600
NOV2A FSRYTIMSSASRDNLTSPG----PLSAQNFRVTHVTIIEVFLHWDPPDPV
gi|12621078| VSAFTIMGEGPPTVLTVRTREQVPSSIQIINYKNISSSSLLLYWDPPEYP
gi|125977| ----------RNVQVRTLSSSTMVITWEPPETP
gi|10728878| ----------RNVQVRTLSSSTMVITWEPPETP
gi|7290546| ----------GFLDDR---SNALHISWEPAETG
gi|1362625| ----------GFLDDP---SNALHISWEPAETG
610 620 630 640 650
NOV2A FFHHYLITILDVENQSKS----IILRTLNSLSLVLIGLKKYTKYKMRVAA
gi|12621078| NGKITHYTIYATELDTNR----AFQMTTVDNSFLITGLKKYTRYKMRVAA
gi|125977| NGQVTGYKVYYTTNSNQPEASWNSQMVDNSELTTVSDVTPHAIYTVRVQA
gi|10728878| NGQVTGYKVYYTTNSNQPEASWNSQMVDNSELTTVSELTPHAIYTVRVQA
gi|7290546| RQDSYRISYHEQTNASEV----PAPFPVAAESQTTTNLTEYTLDSLLAGR
gi|1362625| RQDSYRISYHEQTNASEV----PAPFPVAAESQTTTNLTEYTLDSLLAGR
660 670 680 690 700
NOV2A STHVGESSLSEENDIFVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEK
gi|12621078| STHVGESSLSEENDIFVRTPEDEPESSPQDVQVTGVSPSELRLKWSPPEK
gi|125977| YTSMGAGPMSTP----------
gi|10728878| YTSMGAGPMSTP----------
gi|7290546| RYLIAVQALSKG----------
gi|1362625| RYLIAVQALSKG----------
710 720 730 740 750
NOV2A PNGIIIAYEVLYKNIDTLYMKNTSTTDIILRNLRPHTLYNISVRSYTRFG
gi|12621078| PNGIIIAYEVLYQNADTLFVKNTSTTDLIISDLKPYTLYNISIRSYTRLG
gi|125977| ----------VQVKAQQGVP----------
gi|10728878| ----------VQVKAQQGVP----------
gi|7290546| ----------VASNASDIT---------R-YTRP-
gi|1362625| ----------VASNASDIT---------R-YTRP-
760 770 780 790 800
NOV2A HGNQVSSLLSVRTSESVPDSAPENITYKNISSGEIELSELPPSSPNGIIQ
gi|12621078| HGNQSSSLLSVRTSETVPDSAPENITYKNISSGEIEISELPPRSPNGIIQ
gi|125977| ----------SQPSNFRATDIGETAVTLQWTKPTHSSENIV
gi|10728878| ----------SQPSNFRATDIGETAVTLQWTKPTHSSENIV
gi|7290546| ----------AAPLIQELRSIDQG---LMLSWRSDVNSRQD
gi|1362625| ----------AAPLIQELRSIDQG---LMLSWRSDVNSRQD
810 820 830 840 850
NOV2A KYTIYLKRSNG-NEERTINTTSLTQNIKGLKKYTQYLIEVSASTLKGEGV
gi|12621078| KYTIYLKRSNS-HEARTINTTSLTQTIGGLKKYTHYVIEVSASTLKGEGI
gi|125977| HYELYWNDTYANQAHHKRISNSEAYTLDGLYPDTLYYIWLAARSQRGECA
gi|10728878| HYELYWNDTYANQAHHKRISNSEAYTLDGLYPDTLYYIWLAARSQRGECA
gi|7290546| RYEVHYQRNGT-REERTMATNETSLTIHYLHPGSGYEVKVHAISH---GV
gi|1362625| RYEVHYQRNGT-REERTMATNETSLTIHYLHPGSGYEVKVHAISH---GV
860 870 880 890 900
NOV2A RSAPISLLTEEDAPDSPPQDFSVKQLSGVTVKLSWQPP--LEPNGIILYY
gi|12621078| RSRPISLLTEEDAPDSPPQNFSVKQLSGVTVMLSWQPP--LEPNGIILYY
gi|125977| TTPPIPVRTKQYVPGAPPRNITAIATSSTTISLSWLPPPVERSNGRITYY
gi|10728878| TTPPIPVRTKQYVPGAPPRNITAIATSSTTISLSWLPPPVERSNGRITYY
gi|7290546| RSEPHSYFQAVFP--KPPQNLTLQTVHTNLVVLHWQAP--EGSD-FSEYV
gi|1362625| RSEPHSYFQAVFP--KPPQNLTLQTVHTNLVVLHWQAP--EGSD-FSEYV
910 920 930 940 950
NOV2A TVYVWR----SSLKTIN-VTETSLELSDLDYNVEYSAYVTASTRFGDGKT
gi|12621078| TVYVWDK---SSLRAIN-ATPASLVLSDLDYNVDYGACVTASTRFGDGNA
gi|125977| KVFFVEVGREDDEATTMTINMTSIVLDELKRWTEYKIWVLAGTSVGDG-E


gi|10728878| KVFFVEVGREDDEATTMTLNMTSIVLDELKRWTEYKIWVLAGTSVGDG-P
gi|7290546| VRYRTDA---SPWQRISGLHENEARIKDMHYGERYLVQVNTVS-FGVESP
gi|1362625| VRYRTDA---SPWQRTSGLHENEARIKDMHYGERYLVQVNTVS-FGVESP
960 970 980 990 1000
NOV2A RSNIISFQTPEG-PSDPPKDVYYANLSSSSIILEWTPPS--KPNGIIQYY
gi|12621078| RSSIINFRTPEGEPSDPPNDVHYVNLSSSSIILEWTPPV--KPNGIIQYY
gi|125977| RSHPIILRTQEDVPGD-PQDVKATPLNSTSIHVSWKPPLEKDRNGIIRGY
gi|10728878| RSHPIILRTQEDVPGD-PQDVKATPLNSTSIHVSWKPPLEKDRNGIIRGY
gi|7290546| HPLELNVTMPPQ-----PVSNVVPLVDSRNLTLEWP-----RPDGHVDFY
gi|1362625| HPLELNVTMPPQ-----PVSNVVPLVDSRNLTLEWP-----RPDGHVDFY
1010 1020 1030 1040 1050
NOV2A SVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIIDKLTIFSYYTFWLTAST
gi|12621078| SVYYQNTSGTFVQNFTLLQVTKESDNVTVSARIYRLAIFSYYTFWLTAST
gi|125977| ----------
gi|10728878| ----------
gi|7290546| ----------
gi|1362625| ----------
1060 1070 1080 1090 1100
NOV2A SVGNGNKSSDIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVPPAQPNG
gi|12621078| SVGNGNKSSDIIHVYTDQDIPEGPVGNLTFESISSTAIHVSWEPPSQPNG
gi|125977| ----------HIHAQELRDEG
gi|10728878| ----------HIHAQELRDEG
gi|7290546| -----T----------LKWWPTDEEDR
gi|1362625| -----T----------LKWWPTDEEDR
1110 1120 1130 1140 1150
NOV2A LVFYYVSLILQQTP-RHVRPPLVTYERSIYFDNLEKYTDYILKITPSTEK
gi|12621078| LVFYYLSLNLQQSPPRHMIPPLVTYENSIDFDDLEKYTDYIFKITPSTEK
gi|125977| KGFLNEPFKFDVVD----------TLEFNVTGLQEDTKYSICVAALTRK
gi|10728878| KGFLNEPFKFDVVD----------TLEFNVTGLQEDTKYSIQVAALTRK
gi|7290546| VEFKNVTQLEDLSS-------P---SVRIPIEDLSPGRQYRFEVQASSN-
gi|1362625| VEFKNVTQLEDLSS-------P---SVRIPIEDLSPGRQYRFEVQASSN-
1160 1170 1180 1190 1200
NOV2A GFSDTYTAQLYIKTEEDIPETSPIINTFKNLSSTSVLLSWDPPVKPNGAI
gi|12621078| GFSETYTTQLHIKTEEDVPDTPPIINTFKNLSSTSILLSWDPPLKPNGAI
gi|125977| GDGDRSAAIVVKTPGGVPVRPTVSLKIMEREPIVSLELEWERPAQTYGEL
gi|10728878| GDGDRSAAIVVKTPGGVPVRPTVSLKIMEREPIVSLELEWERPAQTYGEL
gi|7290546| G----------IRSG----------T----------
gi|1362625| G----------IRSG----------T----------
1210 1220 1230 1240 1250
NOV2A ISYDLTL----QGPNENYSFITSDNYTILEELSPFTLYSFFAAARTRKGL
gi|12621078| LGYHLTL----QGPHANHTFVTSGNHIVLEELSPFTLYSFFAAARTMKGL
gi|125977| RGYRIRWGVKDQALKEEMLSGPQMTKKRFDNLERGVEYEFRVAGSNHIGI
gi|10728878| RGYRIRWGVKDQALKEEMLSGPQMTKKRFDNLERGVEYEFRVAGSNHIGI
gi|7290546| ----------THLSTRTMPLIQSDVFIANAGHEQGQ
gi|1362625| ----------THLSTRTMPLIQSDVFIANAGHEQGQ
1260 1270 1280 1290 1300
NOV2A GPSSILEFYTDESVPLAPPQNLTLINCTSDFVWLKWSPSPLPGGIVKVYS
gi|12621078| GPSSILFFYTDESAPLAPPQNLTLINYTSDFVWLTWSPSPLPGGIVKVYS
gi|125977| GQETVKIFQTPEGTPGGPPSNITIRFQTPDVLCVTWDPPTREHRNGIITR
gi|10728878| GQETVKIFQTPEGTPGGPPSNITIRFQTPDVLCVTWDPPTREHRNGIITR
gi|7290546| ----------DETITLSYTPTPADSTRFDIYR
gi|1362625| ----------DETITLSYTPTPADSTRFDIYR
1310 1320 1330 1340 1350
NOV2A FKIHEHETDTIYYKNISGFKTEAKLVGLEPVSTYSIRVSAFTKVGNGNQF


gi|12621078|
gi|125977|
gi|10728878|
gi|7290546|
gi|1362625|
NOV2A
1360 1370 1380 1390 1400
1410 1420 1430 1440 1450
1460 1470 1480 1490 1500
1510 1520 1530 1540 1550
1560 1570 1580 1590 1600
1610 1620 1630 1640 1650
1660 1670 1680 1690 1700
1710 1720 1730 1740 1750


NOV2A
gi|12621078|
gi|125977|
gi|10728878|
gi|7290546|
gi|1362625|
1760 1770 1780 1790 1800
1810 1820 1830 1840 1850
1860 1870 1880 1890 1900
1910 1920 1930 1940 1950
1960 1970 1980 1990 2000
2010 2020 2030 2040 2050
2060 2070 2080 2090 2100


2110 2120 2130 2140 2150
NOV2A NEFIATQGPLPGTVGDFWRMVWETRAKTLVMLTQCFEKGRIRCHQYWPED
gi|12621078| NEFIATQGPLPGTVGDFWRMVWETRTKTLVMLTQCFEKGRIRCHQYWPED
gi|125977| NAYVATQGPLQETFVDFWRMCWELKTATIVMMTRLEERTRIKCDQYWPTR
gi|10728878| NAYVATQGPLQETFVDFWRMCWELKTATIVMMTRLEERTRIKCDQYWPTR
gi|7290546| REFIVTQGPLHSTREEFWRMCWESNSRAIVMLTRCFEKGREKCDQYWPVD
gi|1362625| REFIVTQGPFHSTREEFWRMCWESNSRAIVMLTRCFEKGREKCDQYWPVD
2160 2170 2180 2190 2200
NOV2A NKPVTVFGDIVITKLMEDVQIDWTIRDLKIERH--GDCMTVRQCNFTAWP
gi|12621078| NKPVTVFGDIVITKLMEDIQIDWTIRDLKIERH--GDCMTVRQCNFTGWP
gi|125977| G--TETYGQIFVTTTETQELATYSIRTFQLCRQGFNDRREIKQLQFTAWP
gi|10728878| G--TETYGQIFVTTTETQELATYSIRTFQLCRQGFNDRREIKQLQFTAWP
gi|7290546| R-VAMFYGDIKVQLIIDTHYHDWSISEFMVSRN--CESRIMRHFHFTTWP
gi|1362625| R-VAMFYGDIKVQLIIDTHYHDWSISEFMVSRN--CESRIMRHFHFTTWP
2210 2220 2230 2240 2250
NOV2A EHGVPENSAPLLHFVKLVRASRAHDTTPMIVHCSAGVGRTGVFIALDHLT
gi|12621078| EHGVPENTTPLLHFVKLVRTSRAHDTTPMVVHCSAGVGRTGVFIALDHLT
gi|125977| DHGVPDHPAPFLQFLRRCRALTPPESGPVIVHCSAGVGRTGCYIVIDSML
gi|10728878| DHGVPDHPAPFLQFLRRCRALTPPESGPVIVHCSAGVGRTGCYIVIDSML
gi|7290546| DFGVPEPPQSLVRFVRAFRDVIGTDMRPIIVHCSAGVGRSGTFIALDRIL
gi|1362625| DFGVPEPPLSLVRFVRAFRDVIGTQMRPIIVHCSAGVGRSGTFIALDRII
2260 2270 2280 2290 2300
NOV2A QHINDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILDLLS------
gi|12621078| QHINNHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILDLLS------
gi|125977| ERMKHEKIIDIYGHVTCLRAQRNYMVQTEDQYIFIHDAILEAIICG----
gi|10728878| ERMKHEKIIDIYGHVTCLRAQRNYMVQTEDQYIFIHDAILEAIICG----
gi|7290546| QHIHKSDYVDIFGIVFAMRKERVFMVQTEQQYVCIHQCLLAVLEGKEHLL
gi|1362625| QHIHKSDYVDIFGIVFAMRKERVFMVQTEQQYVCIHQCLLAVLEGKEHLL
2310 2320 2330 2340 2350
NOV2A ---------NKGSNQPICFVNYSALQKMDSLDAMEGGDVELEWEETTM---
gi|12621078| ---------NKGGHQPVCFVNYSTLQKMDSLDAMEG-DVELEWEETTM---
gi|125977| --VTEVPARNLHTHLQKLLITEPGETISGMEVEFKKLSNVKMDSSKFVTA
gi|10728878| --VTEVPARNLHTHLQKLLITEPGETISGMEVEFKKLSNVKMDSSKFVTA
gi|7290546| ADSLELHANDGYEVTKIYLERQPQTKMGTLPIRASLAMAEKLDADLMTNK
gi|1362625| ADSLELHANDGYEVTKIYLERQPQTKMGTLPIRASLAMAEKLDADLMTNK
2360 2370 2380 2390 2400
NOV2A ----------
gi|12621078| ----------
gi|125977| NLPCNKHKNRLVHILPYESSRVYLTPIHGIEGSDYVNASFIDGYRYRSAY
gi|10728878| NLPCNKHKNRLVHILPYESSRVYLTPIHGIEGSDYVNASFIDGYRYRSAY
gi|7290546| DEDEDQEQQQQQQIQ----------LATEVKPKGSN
gi|1362625| DEDEDQEQQQQQQLQ----------LATEVKPKGSN
2410 2420 2430 2440 2450
NOV2A ----------
gi|12621078| ----------
gi|125977| IAAQGPVQAAEDFWRMLWEHNSTIVVMLTKLKEMGREKCFQYWPHERSV
gi|10728878| IAAQGPVQAAEDFWRMLWEHNSTIVVMLTKLKEMGREKCFQYWPHERSV
gi|7290546| DDEEDEEDDDDDDDQQPLNNETTATLSSASCSSS---------THDVHV
gi|1362625| DDEEDEEDDDDDDDQQPLNNETTATLSSASCSSS---------THDVHV
2460 2470 2480 2490 2500
NOV2A ----------
gi|12621078| ----------
gi|125977| RYQYYVVDPIAEYNMPQYKLREFKVTDARDGSSRTVRQFQFIDWPEQGVP
gi|10728878| RYQYYVVDPIAEYNMPQYKLREFKVTDARDGSSRTVRQFQFIDWPEQGVP

```
gi|7290546|   VLQEATEKPKQEQERICAGTQSHADTESDNTDSDDDDEDGDGKVAKDGAV
gi|1362625|   VLQEATEKPKQEQERICAGTQSHADTESDNTDSDDDDEDGDGKVAKDGAV

                      2510      2520      2530      2540      2550
              ....|....|....|....|....|....|....|....|....|....|
NOV2A         ----------------------------------------------------
gi|12621078|  ----------------------------------------------------
gi|125977|    KSGEGFIDFIGQVHKTKEQFGQDGPITVHCSAGVGRSGVFITLSIVLERM
gi|10728878|  KSGEGFIDFIGQVHKTKEQFGQDGPITVHCSAGVGRSGVFITLSIVLERM
gi|7290546|   ADEDGWWY----------------------------------------
gi|1362625|   ADEDGWWY----------------------------------------

                      2560      2570      2580      2590
              ....|....|....|....|....|....|....|....|....|...
NOV2A         ---------------------------------------------
gi|12621078|  ---------------------------------------------
gi|125977|    QYEGVLDVFQTVRILRSQRPAMVQTEDQYHFCYRAALEYLGSFDNYTN
gi|10728878|  QYEGVLDVFQTVRILRSQRPAMVQTEDQYHFCYRAALEYLGSFDNYTN
gi|7290546|   ---------------------------------------------
gi|1362625|   ---------------------------------------------
```

Tables 2J-2EE list the domain descriptions from DOMAIN analysis results against NOV2a. This indicates that the NOV2a sequence has properties similar to those of other proteins known to contain this domain.

Table 2J. Domain Analysis of NOV2a

gnl|Smart|smart00194, PTPc, Protein tyrosine phosphatase, catalytic domain (SEQ ID NO:93)
CD-Length = 264 residues, 99.6% aligned
Score = 318 bits (816), Expect = 2e-87

```
NOV 1:   1983  KFQEEFSELPK-FLQDLSSTDADLPWNRAKNRFPNIKPYNNNRVKLIADASVPGSDYINA  2041
Sbjct:   1     GLEEEFEKLQRLTPDDLSCTVAILPENRDKNRYKDVLPYDHTRVKL-KPPPGEGSDYINA  59

NOV 1:   2042  SYISGYLCPNEFIATQGPLPGTVGDFWRMVWETRAKTLVMLTQCFEKGRIRCHQYWPEDN  2101
Sbjct:   60    SYIDGPNRPKAYIATQGPLPSTVEDFWRMVWEEKVPVIVMLTELVEKGREKCAQYWPEKE  119

NOV 1:   2102  KPVTVFGDIVITKLMEDVQIDWTIRDLKIERHG--DCMTVRQCNFTAWPEHGVPENSAPL  2159
Sbjct:   120   GGSLTYGDITVTLKSVEKVDDYTIRTLEVTNTGGSETRTVTHYHYTNWPDHGVPESPKSL  179

NOV 1:   2160  IHFVKLVRASRAH--DTTPMIVHCSAGVGRTGVFIALDHLTQHINDHDFVDIYGLVAELR  2217
Sbjct:   180   LDLVRAVRKSQSTLRNSGPIVVHCSAGVGRTGTFIAIDILLQQLEAGKEVDIFEIVKELR  239

NOV 1:   2218  SERMCMVQNLAQYIFLHQCILDLL  2241
Sbjct:   240   SQRPGMVQTEEQYIFLYRAILEYL  263
```

Table 2K. Domain Analysis of NOV2a

gnl|Pfam|pfam00102, Y_phosphatase, Protein-tyrosine phosphatase (SEQ ID NO:94)
CD-Length = 235 residues, 100.0% aligned
Score = 275 bits (704), Expect = 2e-74

```
NOV 1:  2008  NRAKNRFPNIKPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGPLPGTVGDF  2067
              |+ |||+ ++ ||++ ||||        ||||||||+ ||  |  +|||||||| |+ ||
Sbjct:  1     NKEKNRYKDVLPYDHTRVKL-KPLGDEDSDYINASYVDGYKKPKAYIATQGPLPNTIEDF  59

NOV 1:  2068  WRMVWETRAKTLVMLTQCFEKGRIRCHQYWPEDNKPVTVFGDI-VITKLMEDVQIDWTIR  2126
              |||||| + + +||||+  |||| +| |||||       +||  |    +|  + |+|+|
Sbjct:  60    WRMVWEEKVRVIVMLTELVEKGREKCAQYWPEKEGGSLTYGDFTVTCVSVEKKKDDYTVR  119

NOV 1:  2127  DLKIERHGDC--MTVRQCNFTAWPEHGVPENSAPLIHFVKLVRASRAH-DTTPMIVHCSA  2183
               |++   ||    ||+  ++| ||+|||||+   ++  ++ || |+   |  |++|||||
Sbjct:  120   TLELTNSGDDETRTVKHYHYTGWPDHGVPESPKSILDLLRKVRKSKGTPDDGPIVVHCSA  179

NOV 1:  2184  GVGRTGVFIALDHLTQHINDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILD  2239
              |+|||| |||+| | | +     ||++  | +|||+|  |||   ||||++  ||+
Sbjct:  180   GIGRTGTFIAIDILLQQLEKEGVVDVFDTVKKLRSQRPGMVQTEEQYIFIYDAILE  235
```

Table 2L. Domain Analysis of NOV2a

gnl|Smart|smart00404, PTPc_motif, Protein tyrosine phosphatase, catalytic domain motif (SEQ ID NO:95)
CD-Length = 105 residues, 100.0% aligned
Score = 120 bits (301), Expect = 8e-28

```
NOV 1:  2138  TVRQCNFTAWPEHGVPENSAPLIHFVKLVRASRAH--DTTPMIVHCSAGVGRTGVFIALD  2195
              ||+  ++| ||+|||||+   ++ |++ |+ |     +  |++|||||||||||| |+|+|
Sbjct:  1     TVKHYHYTGWPDHGVPESPDSILEFLRAVKKSLNKSANNGPVVVHCSAGVGRTGTFVAID  60

NOV 1:  2196  HLTQHI-NDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILD  2239
               | | +      |||+ +| ||||+|   || | ||+||++ +|+
Sbjct:  61    ILLQQLEAGTGEVDIFDIVKELRSQRPGAVQTLEQYLFLYRALLE  105
```

Table 2M. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 100.0% aligned
Score = 60.8 bits (146), Expect = 8e-10

```
NOV 1:  54    PGPPVFLAGERVGSAGILLSWNTPPNPNGRIISYIVKYKEVCPWMQTVYTQVRSKPDSLE  113
              |  |  |    | |  + |||+ ||+ || |  | |+|+ |       + ++     +
Sbjct:  1     PSAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNS--GEEWNEITVPGTTTS  58

NOV 1:  114   VLLTNLNPGTTYEIKVAAENSAGIGVFS  141
               || | ||| ||++| | |  | | |
Sbjct:  59    YTLTGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2N. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 95.3% aligned
Score = 58.9 bits (141), Expect = 3e-09

```
NOV 1:  659   SSPQDVEVIDVTADEIRLKWSPPEKPNGIIIAYEVLYKNIDTLYMKNT-----STTDIIL  713
              |+| ++ | |||+  + | ||||   || |  ||| |+ +++    |      +||   |
Sbjct:  2     SAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL  61

NOV 1:  714   RNLRPHTLYNISVRSYTRFGHG  735
                |+| | | + |++    |+|
Sbjct:  62    TGLKPGTEYEVRVQAVNGGGNG  83
```

Table 2O. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 100.0% aligned
Score = 57.0 bits (136), Expect = 1e-08

```
NOV 1:  1330  PDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMVTV-------ERNSTKVSPQDHMYT  1382
              |    |+     +  |+ + | ||   || || | |         | |   |       ||
Sbjct:  1     PSAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYT  60

NOV 1:  1383  FIKLLANTSYVFKVRASTSAGEGDES  1408
                |   | |  +|+|    | |  |
Sbjct:  61    LTGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2P. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 98.8% aligned
Score = 53.1 bits (126), Expect = 2e-07

```
NOV 1:  753   SAPENITYKNISSGEIELSFLPPSSPNGIIQKYTIYLKRSNGNE---ERTINTTSLTQNI  809
              ||| |+|  +++|  + ||+ ||   || |  | +  +  |  |   | |+  |+ +  +
Sbjct:  2     SAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL  61

NOV 1:  810   KGLKKYTQYIIEVSASTLKGEGVRS  834
               |||  |+| + | |    | |  |
Sbjct:  62    TGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2Q. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 95.3% aligned
Score = 52.4 bits (124), Expect = 3e-07

```
NOV 1:  848   SPPQDFSVKQLSGVTVKLSWQPPLEPNGIILYYTVYVWR----SSLKTINV--TETSLEL  901
              | | + +|  ++  ++ ||| || + || |  | |             | |  | ||  |
Sbjct:  2     SAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL  61

NOV 1:  902   SDLDYNVEYSAYVTASTRFGDG  923
              + |    ||   | |    |+|
Sbjct:  62    TGLKPGTEYEVRVQAVNGGGNG  83
```

Table 2R. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 91.9% aligned
Score = 51.6 bits (122), Expect = 5e-07

```
NOV 1:  1148  TFKNLSSTSVLLSWDPPVKPNGAIISYDLTLQGPNENYSFIT-----SDNYIILEELSPF  1202
              |  +++|||+ ||| ||   || |  |++  |  |    +       +     |  | |
Sbjct:  8     TVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTLTGLKPG  67

NOV 1:  1203  TLYSFFAAARTRKGLGPSS  1221
              | |     |    | || |
Sbjct:  68    TEYEVRVQAVNGGGNGPPS  86
```

Table 2S. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 94.2% aligned
Score = 51.2 bits (121), Expect = 6e-07

```
NOV 1:  1235  PPQNLTLINCTSDFVWLKWSPSPLPGGIVKVYSFK-IHEHETDTIYYKNISGFKTEAKLV  1293
               | |||+ + ||  + | ||| |   | +  |  +   +  +      + |  |   |
Sbjct:  3     APTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTLT  62

NOV 1:  1294  GLEPVSTYSIRVSAFTKVGNG  1314
              ||+| + | +|| |    |||
Sbjct:  63    GLKPGTEYEVRVQAVNGGGNG  83
```

Table 2T. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 100.0% aligned
Score = 49.7 bits (117), Expect = 2e-06

```
NOV 1:  1420  PSVPTNIAFSDVQSTSATLTWIRPDTILGYFQNYKITTQLRAQKCKEWESEECVEYQKIQ  1479
              || |||+  +|| ||| ||+|  |    |    |++  |           ||  |
Sbjct:  1     PSAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQ------PVNSGEEWNEITV--  52

NOV 1:  1480  YLYEAHLTEETVYGLKKFRWYRFQVAASTNAGYGNAS  1516
                    |  |+ |||    |  +| |    | |  |
Sbjct:  53    ---PGTTTSYTLTGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2U. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 98.8% aligned
Score = 47.4 bits (111), Expect = 9e-06

```
NOV 1:  940   DPPKDVYYANLSSSSIILFWTPPSKPNGIIQYYSVYYRNT-SGTFMQNFTLHEVTNDFDN  998
               | ++   +++|+|+ | |+||   || |  | | |+   ||      |+   |
Sbjct:  2     SAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTT----  57

NOV 1:  999   MTVSTIIDKLTIFSYYTFWLTASTSVGNGNKS  1030
```

```
                 |  +  |    +  |    +  |     |||  |
Sbjct:  58     ---SYTLTGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2V. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 91.9% aligned
Score = 47.0 bits (110), Expect = 1e-05

```
NOV 1:  1530  GPPENVHVVATSPFSISISWSEPAVITGP-TCYLIDVKSVDNDEFNISFIKSNEENKTIE  1588
                | |+ |    +  |+++||| |     || | | ++ + |++ |             +
Sbjct:  2     SAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTT-SYT  60

NOV 1:  1589  IKDLEIFTRYSVVITAFTGN  1608
              +  |+  | | | + |  |
Sbjct:  61    LTGLKPGTEYEVRVQAVNGG  80
```

Table 2W. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 96.5% aligned
Score = 46.6 bits (109), Expect = 2e-05

```
NOV 1:  1633  DPPNNMTFQKIPDEVTKFQLTFLPPSQPNGNIQVYQALVYREDDPTAVQIHNLSIIQKTN  1692
                | |+|   +    |   |++ ||   || |  |+      +         +    +
Sbjct:  2     SAPTNLTVTDVTS--TSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTS-  58

NOV 1:  1693  TFVIAMLEGLKGGHTYNISVYAVNSAGAGP  1722
                    | ||| |  | + | |||  | ||
Sbjct:  59    ----YTLTGLKPGTEYEVRVQAVNGGGNGP  84
```

Table 2X. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 98.8% aligned
Score = 44.7 bits (104), Expect = 6e-05

```
NOV 1:  303   GPPQNCVTGNITGKSFSILWDPPTIVTGKFS-YRVELY---GPSAGRILDNSTKDLKFAF  358
                | |    ++|  | ++ | ||    |  + | ||           +       +
Sbjct:  2     SAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL  61

NOV 1:  359   TNLTPFTMYDVYIAAETSAGTGPKS  383
              | | | | |+| + |    | || |
Sbjct:  62    TGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2Y. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 100.0% aligned
Score = 43.1 bits (100), Expect = 2e-04

```
NOV 1:  561   PLSAQNFRVTHVTITEVFLHWDPPDPVF--FHHYLITILDVENQSKSIILRTLNSLSLVL  618
              | +  |  || || | + | | ||         | +    | +  +   +    + +
Sbjct:  1     PSAPTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYT  60
```

```
NOV 1:  619   I-GLKKYTKYKMRVAASTHVGESSLS  643
              + |||  |+|++|| |    |    |
Sbjct:  61    LTGLKPGTEYEVRVQAVNGGGNGPPS  86
```

Table 2Z. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
CD-Length = 86 residues, 93.0% aligned
Score = 38.5 bits (88), Expect = 0.004

```
NOV 1:  1047  VGNLTYESISSTAINVSWVPPAQPNGLVFYY-VSLILQQTPRHVRPPLVT-YERSIYFDN  1104
                |||   ++||++ +|| ||   || +  | |      +        |     |
Sbjct:  4     PTNLTVTDVTSTSLTLSWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTLTG  63

NOV 1:  1105  LEKYTDYILKITPSTEKGFS  1124
              |+  |+| +++       |
Sbjct:  64    LKPGTEYEVRVQAVNGGGNG  83
```

Table 2AA. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 96.4% aligned
Score = 54.7 bits (130), Expect = 6e-08

```
NOV 1:  54    PGPPVFLAGERVGSAGILLSWNTPPNP-NGRIISYIVKYKEVCPWMQTVYTQVRSKPDSL  112
              | ||  |    | |  + |||  ||+   | |+ | |+|+|   | +   |       +
Sbjct:  1     PSPPSNLRVTDVTSTSVTLSWEPPPDDITGYIVGYRVEYREEGEWKEVNVTP----SSTT  56

NOV 1:  113   EVLLTNLNPGTTYEIKVAAENSAG  136
                 || | ||| || +| | |
Sbjct:  57    SYTLTGLKPGTEYEFRVRAVNGEA  80
```

Table 2BB. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 92.8% aligned
Score = 52.8 bits (125), Expect = 2e-07

```
NOV 1:  659   SSPQDVEVIDVTADEIRLKWSPPEKP-NGIIIAYEVLYKNID---TLYMKNTSTTDIILR  714
              | | ++ | |||+  + | | ||     | |+ | | |+       + +  +|||   |
Sbjct:  2     SPPSNLRVTDVTSTSVTLSWEPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTLT  61

NOV 1:  715   NLRPHTLYNISVRSYTR  731
               |+| | |   ||+
Sbjct:  62    GLKPGTEYEFRVRAVNG  78
```

Table 2CC. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 94.0% aligned
Score = 45.4 bits (106), Expect = 3e-05

```
NOV 1:  1235  PPQNLTLINCTSDFVWLKWSPSPLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVG  1294
              || || + + ||  | | | | |       |     +  | +           |   | |
Sbjct:  3     PPSNLRVTDVTSTSVTLSWEPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTLTG  62

NOV 1:  1295  LEPVSTYSIRVSAFTKVG  1312
              |+| + |  || |
Sbjct:  63    LKPGTEYEFRVRAVNGEA  80
```

Table 2DD. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 100.0% aligned
Score = 42.7 bits (99), Expect = 2e-04

```
NOV 1:  561   PLSAQNFRVTHVTITEVFLHWDPPDPVFFHHYLITILDVENQSKSIILRTLNS--LSLVL  618
              |    | ||| || | | | |+||      + +   ++   + +   +    |   | |
Sbjct:  1     PSPPSNLRVTDVTSTSVTLSWEPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTL  60

NOV 1:  619   IGLKKYTKYKMRVAASTHVGESS  641
               |||  |+|+ || |
Sbjct:  61    TGLKPGTEYEFRVRAVNGEAGEG  83
```

Table 2EE. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 92.8% aligned
Score = 41.2 bits (95), Expect = 7e-04

```
NOV 1:  848   SPPQDFSVKQLSGVTVKLSWQPPLEP-NGIILYYTVYVWRSS----LKTINVTETSLELS  902
              ||| +  |  ++  +| |||+|| +   | |+ | |          +     + ||  |+
Sbjct:  2     SPPSNLRVTDVTSTSVTLSWEPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTLT  61

NOV 1:  903   DLDYNVEYSAYVTASTR  919
               |    ||   | |
Sbjct:  62    GLKPGTEYEFRVRAVNG  78
```

Receptor tyrosine phosphatases (rPTPs) are part of the signaling cascades that control cell survival, proliferation and differentiation. The novel protein tyrosine phosphatase described in the application contains a phosphatase domain and thirteen fibronectin type III repeats. It closely resembles rPTP-GMC1, a rat membrane phosphatase that is expressed in kidney glomerulus and is upregulated in response to kidney injury (Wright et.al. J Biol Chem 1998 Sep 11;273(37):23929-37). Tissue specificity of PTPs varies widely ; for eg rPTP-GMC1 is expressed by mesangial cells in the kidney while GLEPP1 (another membrane phosphatase) is expressed by podocytes in the kidney (Thomas et. al. ; J Biol Chem 1994 Aug 5;269(31):19953-62). Tappia et. al. demonstrated expression of a PTP in the liver could regulate the activity of the insulin and EGF receptors (Tappia et. al.; Biochem J 1993 May 15;292 (Pt 1):1-5).A number of phosphatases have been demonstrated to play a role in cancer, for eg. PTP zeta; a membrane phosphatase; is expressed in brain and is also expressed by a glioblastoma cell line (Krueger et. al.; Proc Natl Acad Sci U S A 1992 Aug 15;89(16):7417-21); rPTP alpha is expressed in breast tumors and correlates with tumor grade (Ardini et. al.; Oncogene 2000 Oct 12;19(43):4979-87). This phosphatase (rPTP alpha) is also expressed by human prostate cancer cell lines, oral squamous cell carcinoma and was correlated with histological grade of the oral tumor (Zelivianski et. al.; Mol Cell Biochem 2000 May;208(1-2):11-8; Berndt et al.; Histochem Cell Biol 1999 May;111(5):399-403). PTP-1B has been suggested to play arole in diabetes and obesity (Kennedy et. al.; Biochem Pharmacol 2000 Oct 1;60(7):877-83) whle mutations in a PTP named EPM2A have been suggested as the cause of Lafora's disease (and autosomal recessive form of progressive myoclonus epilepsy) (Minassian et. al. Nat Genet 1998 Oct;20(2):171-4). Given the wide ranging effects of this family of proteins , we hypothesize that the novel protein described in this application plays a role in cancer, neurological, immune and metabolic diseases.

The disclosed NOV2 nucleic acid of the invention encoding a Protein tyrosine phosphatase precursor-like protein includes the nucleic acid whose sequence is provided in Table 2A, 2C, or 2E or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 2A, 2C, or 2E while still encoding a protein that maintains its Protein tyrosine phosphatase precursor like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications

include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 16 percent of the bases may be so changed.

The disclosed NOV2 protein of the invention includes the Protein tyrosine phosphatase precursor-like protein whose sequence is provided in Table 2B, 2D, or 2F. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 2B, 2D, or 2F while still encoding a protein that maintains its Protein tyrosine phosphatase precursor-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 18 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this Protein tyrosine phosphatase precursor-like protein (NOV2) may function as a member of a "Protein tyrosine phosphatase precursor family". Therefore, the NOV2 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV2 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the Protein tyrosine phosphatase precursor-like protein (NOV2) may be useful in gene therapy, and the Protein tyrosine phosphatase precursor -like protein (NOV2) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cancer, kidney cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, nephrological disesases including diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis,

glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, Lesch-Nyhan syndrome, Hirschsprung's disease , Crohn's Disease, appendicitis, or other pathologies or conditions. The NOV2 nucleic acid encoding the Protein tyrosine phosphatase precursor-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV2 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV2 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV2 proteins have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV2 epitope is from about amino acids 1 to 100. In another embodiment, a NOV2 epitope is from about amino acids 200 to 300. In further embodiments, a NOV2 epitope is from about amino acids 450 to 500, from about amino acids 600 to 900, from about amino acids 950 to 1000, from about amino acids 1200 to 1300, from about amino acids 1400 to 1600, from about amino acids 1800 to 1900, from about amino acids 1950 to 2050, and from about amino acids 2200 to 2300. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV3

A disclosed NOV3 nucleic acid of 4538 nucleotides (also referred to as 134899552_EXT) encoding a novel human homolog of the *Drosophila* pecanex-like protein is shown in Table 3A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 101-103 and ending with a TGA codon at nucleotides 4439-4441. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 3A, and the start and stop codons are in bold letters.

Table 3A. NOV3 nucleotide sequence (SEQ ID NO:11).

CATGAAGGAAAAATTCTGAGTATTCTAATGGCTTTTTAAAATAATCATTTATTTGCTAGGTAAGTTCTCTTC
TACGCTGTATGAGACTGGTGGCTGTGAT**ATG**TCACTTGTGAATTTTGAACCAGCAGCAAGAAGAGCATCCAA
TATCTGGGACACAGATTCTCATGTATCCAGTTCTACCTCAGTTCGATTTTATCCACATGATGTGATTCGATT
GAATAGACTATTGACCATTGATACAGATTTGTTGGAGCAACAGGACATTGATCTAAGCCCTGACTTGGCAGC
TACTTACGGCCCAACAGAAGAAGCTGCCCAAAAGGTTAAACACTATTATCGCTTTTGGATCCTACCCCAGCT
GTGGATTGGCATTAACTTTGACAGACTCACACTTTTGGCCCTGTTTGATAGGAATCGTGAGATCCTGGAAAA
TGTGTTAGCTGTCATCCTGGCTATTCTCGTGGCCTTTTTGGGATCTATTCTTCTCATACAAGGATTCTTCAG
AGATATCTGGGTCTTCCAGTTCTGCCTCGTCATAGCCAGCTGTCAATACTCACTGCTTAAGAGTGTTCAACC

AGATTCTTCTTCTCCCAGACATGGTCATAATCGTATCATTGCCTACAGTAGACCAGTTTATTTCTGCATATG
TTGCGGTCTTATTTGGCTCTTGGATTATGGTAGCAGAAACCTGACTGCAACCAAGTTCAAATTATATGGAAT
AACTTTCACCAATCCACTGGTGTTTATATCAGCCAGGGATTTAGTTATAGTGTTTACACTCTGTTTCCCAAT
AGTGTTTTTCATTGGTCTCCTGCCTCAGGTGAATACATTTGTAATGTACCTTTGTGAACAATTGGATATTCA
TATTTTTGGTGGTAATGCCACTACAAGCCTGCTTGCAGCACTTTACAGTTTTATCTGTAGCATTGTTGCAGT
AGCCTTATTGTATGGATTATGTTATGGGGCTTTACAGGATTCTTGGGATGGCCAGCATATTCCAGTACTTTT
CTCCATTTTTTGTGGTTTATTAGTGGCAGTGTCTTACCATCTCAGCCGACAAAGCAGTGATCCATCTGTACT
TAGCTCTTTAGTGCAATCCAAGATTTTTCCAAAAACGGAAGAGAAAAATCCAGAAGACCCTCTATCTGAAGT
AAAAGATCCACTGCCTGAAAAACTTAGAAATTCTGTTAGTGAGCGATTACAGTCTGACCTGGTAGTATGCAT
TGTAATTGGTGTGCTGTATTTTGCTATTCATGTAAGCACAGTCTTCACAGTATTGCAGCCTGCCCTCAAGTA
TGTGTTGTATACATTGGTTGGCTTTGTGGGTTTTGTAACCCATTATGTGCTGCCTCAAGTTAGAAAACAGCT
ACCATGGCACTGTTTCTCTCATCCTCTGCTAAAGACACTAGAGTATAATCAGTATGAAGTTCGAGATGCAGC
CACTATGATGTGGTTTGAGAAACTTCATGTGTGGCTTCTTTTTGTGGAGAAGAATATAATCTATCCATTGAT
TGTTCTCAATGAACTGAGCAGCAGTGCAGAGACAATTGCTAGTCCAAAGAAACTGAATACAGAGTTAGGTGC
TTTAATGATCACTGTTGCTGGTTTGAAGTTGCTACGATCCTCTTTTAGCAGCCCTACATATCAGTATGTTAC
AGTCATCTTTACTGTGCTGTTTTTCAAATTTGACTATGAAGCTTTTTCAGAGACCATGCTGTTGGATCTCTT
CTTTATGTCCATACTCTTCAACAAGCTTTGGGAACTACTTTATAAATTGCAGTTTGTGTATACCTATATTGC
CCCATGGCAGATCACATGGGGTTCTGCTTTCCATGCTTTTGCTCAGCCTTTTGCAGTGCCTCGTTCAGCCAT
GCTGTTTATTCAGGCTGCTGTCTCGGCCTTCTTCTCTACTCCACTGAACCCCTTTCTGGGAAGTGCAATATT
CATCACTTCATATGTCCGACCTGTGAAATTCTGGGAGAGAGACTATAGCACAAAACGAGTGGATCATTCAAA
TACCAGATTGGCTTCCCAGCTTGATAGAAATCCAGGTTCAGATGACAACAATCTGAATTCCATCTTTTATGA
GCATTTAACTAGATCCCTACAGCACAGCCTCTGTGGTGATTTGCTACTAGGACGGTGGGGAAACTACAGTAC
AGGGGACTGTTTCATCCTTGCCTCTGACTATCTCAATGCATTAGTACACCTTATAGAGATAGGCAATGGTCT
GGTCACTTTTCAGCTGCGGGGACTTGAATTCAGAGGTACCTACTGTCAACAACGGGAAGTGGAGGCCATTAC
TGAAGGTGTAGAGGAAGATGAAGGATTTTGCTGTTGTGAACCTGGCCATATTCCTCACATGCTTTCATTTAA
TGCTGCATTTAGCCAGCGATGGCTAGCTTGGGAAGTGATAGTCACAAAGTACATTCTGGAGGGTTATAGCAT
CACTGATAACAGTGCTGCTTCTATGCTTCAAGTCTTTGATCTTCGGAAAGTACTCACCACTTACTATGTCAA
GGGTATCATTTATTATGTTACGACCTCGTCTAAGCTAGAGGAGTGGCTAGCTAATGAGACAATGCAGGAAGG
ACTTCGTCTGTGTGCTGATCGCAATTATGTCGATGTGGACCCGACCTTTAATCCAAACATTGATGAAGACTA
TGACCACCGACTGGCAGGCATATCTAGGGAGAGTTTCTGTGTGATTTACCTCAACTGGATAGAGTACTGCTC
TTCCCGAAGAGCAAAGCCTGTGGATGTGGACAAAGATTCATCCCTAGTGACTCTCTGTTATGGACTCTGTGT
TCTGGGACGGAGAGCTTTGGGGACTGCATCCCATCATATGTCCAGTAATTTAGAGTCATTCCTCTATGGATT
GCATGCCCTATTTAAAGGAGATTTCCGTATTTCTTCAATTCGAGATGAATGGATCTTTGCTGACATGGAATT
GCTAAGAAAAGTAGTAGTCCCTGGGATCCGTATGTCCATTAAACTTCATCAGGATCATTTTACTTCTCCAGA
TGAATATGATGACCCTACTGTGCTCTATGAAGCCATAGTATCTCATGAGAAGAACCTCGTAATAGCCCATGA
AGGGGACCCTGCATGGCGGAGTGCAGTACTTGCCAACTCTCCCTCCTTGCTTGCTCTGCGGCATGTCATGGA
TGATGGCACCAATGAATATAAAATCATCATGCTCAACAGACGCTACCTGAGCTTCAGGGTCATTAAAGTGAA
TAAGGAATGTGTCCGAGGTCTTTGGGCAGGGCAACAGCAGGAGCTTGTTTTTCTACGTAACCGTAACCCAGA
GAGAGGTAGCATCCAAAATGCAAAGCAAGCCCTGAGAAACATGATAAACTCATCTTGTGATCAACCTATTGG
CTACCCAATCTTTGTCTCACCCCTGACAACTTCTTACTCTGACAGCCACGAACAGCTTAAAGACATTCTTGG
GGGTCCTATCAGCTTGGGAAATATCAGGAACTTCATAGTGTCAACCTGGCACAGGCTTAGGAAAGGTTGCGG
AGCTGGATGTAACAGTGGTGGCAATATTGAAGATTCTGATACTGGAGGTGGGACTTCCTGCACTGGTAACAA
TGCAACAACTGCCAACAATCCCCACAGCAACGTGACCCAGGGAAGCATTGGAAATCCTGGGCAGGGATCAGG
AACTGGACTCCACCCACCTGTCACATCTTATCCTCCAACACTAGGTACTAGCCACAGCTCTCACTCTGTGCA
GTCGGGCCTGGTCAGACAGTCTCCTGCCCGGGCCTCAGTAGCCAGCCAGTCTTCCTACTGCTATAGCAGCCG
GCATTCATCCCTCCGGATGTCCACCACTGGGTTTGTGCCTTGTCGGCGCTCTTCTACTAGTCAGATATCGCT
TCGAAACTTGCCATCATCCATCCAATCCCGACTGTCGATGGTGAACCAAATGGAACCCTCAGGTCAGAGCGG
CCTGGCCTGTGTGCAGCACGGCCTGCCTTCCTCCAGCAGCTCCAGCCAAAGCATCCCAGCCTGCAAACATCA
CACTCTCGTGGGCTTTCTTGCGACAGAGGGAGGTCAGAGCAGTGCCACTGATGCACAGCCAGGCAACACCTT
AAGTCCTGCCAACAATTCACACTCCAGAAAGGCAGAAGTGATTTACAGAGTCCAAATTGTGGATCCCAGTCA
AATTCTGGAAGGGATCAACCTGTCTAAAAGGAAAGAGCTACAGTGGCCTGATGAAGGAATCCGGTTAAAAGC
TGGGAGAAATAGCTGGAAAGACTGGAGTCCGCAGGAGGGCATGGAAGGCCATGTGATTCACCGATGGGTGCC
TTGCAGCAGAGATCCAGGTACCAGATCCCACATCGACAAGGCAGTGCTTCTGGTCCAGATTGATGATAAATA
TGTGACTGTAATTGAAACTGGGGTACTAGAACTTGGGGCTGAAGTGTGAGCCAGTGTTTATTATAAAGACAT
TTCTTTTTCCCTCTCAATTCCAAGGCATTGGAAAAAGAGAGGAACAAGCAGAAGATGCCTGCAGGTATCACT
TT

The disclosed NOV3 nucleic acid sequence, localized to chromsome 14, has 2277 of 2283 bases (99%) identical to a gb:GENBANK-ID:AB018348|acc:AB018348.1 mRNA from *Homo sapiens* (*Homo sapiens* mRNA for KIAA0805 protein, partial cds) (E = 0.0).

A NOV3 polypeptide (SEQ ID NO:12) encoded by SEQ ID NO:11 has 1446 amino acid residues and is presented using the one-letter code in Table 3B. Signal P, Psort and/or Hydropathy results predict that NOV3 does not contain a signal peptide and is likely to be

localized to the plasma membrane with a certainty of 0.8000. In other embodiments, NOV3 may also be localized to the mitochondrial inner membrane with a certainty of 0.4714, the Golgi body with a certainty of 0.4000, or the endoplasmic reticulum (membrane) with a certainty of 0.3000.

Table 3B. Encoded NOV3 protein sequence (SEQ ID NO:12).

```
MSLVNFEPAARRASNIWDTDSHVSSSTSVRFYPHDVIRLNRLLTIDTDLLEQQDIDLSPDLAATYGPTEEAA
QKVKHYYRFWILPQLWIGINFDRLTLLALFDRNREILENVLAVILAILVAFLGSILLIQGFFRDIWVFQFCL
VIASCQYSLLKSVQPDSSSPRHGHNRIIAYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGITFTNPLVFI
SARDLVIVFTLCFPIVFFIGLLPQVNTFVMYLCEQLDIHIFGGNATTSLLAALYSFICSIVAVALLYGLCYG
ALQDSWDGQHIPVLFSIFCGLLVAVSYHLSRQSSDPSVLSSLVQSKIFPKTEEKNPEDPLSEVKDPLPEKLR
NSVSERLQSDLVVCIVIGVLYFAIHVSTVFTVLQPALKYVLYTLVGFVGFVTHYVLPQVRKQLPWHCFSHPL
LKTLEYNQYEVRDAATMMWFEKLHVWLLFVEKNIIYPLIVLNELSSSAETIASPKKLNTELGALMITVAGLK
LLRSSFSSPTYQYVTVIFTVLFFKFDYEAFSETMLLDLFFMSILFNKLWELLYKLQFVYTYIAPWQITWGSA
FHAFAQPFAVPRSAMLFIQAAVSAFFSTPLNPFLGSAIFITSYVRPVKFWERDYSTKRVDHSNTRLASQLDR
NPGSDDNNLNSIFYEHLTRSLQHSLCGDLLLGRWGNYSTGDCFILASDYLNALVHLIEIGNGLVTFQLRGLE
FRGTYCQQREVEAITEGVEEDEGFCCCEPGHIPHMLSFNAAFSQRWLAWEVIVTKYILEGYSITDNSAASML
QVFDLRKVLTTYYVKGIIYYVTTSSKLEEWLANETMQEGLRLCADRNYVDVDPTFNPNIDEDYDHRLAGISR
ESFCVIYLNWIEYCSSRRAKPVDVDKDSSLVTLCYGLCVLGRRALGTASHHMSSNLESFLYGLHALFKGDFR
ISSIRDEWIFADMELLRKVVVPGIRMSIKLHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAWRSAV
LANSPSLLALRHVMDDGTNEYKIIMLNRRYLSFRVIKVNKECVRGLWAGQQQELVFLRNRNPERGSIQNAKQ
ALRNMINSSCDQPIGYPIFVSPLTTSYSDSHEQLKDILGGPISLGNIRNFIVSTWHRLRKGCGAGCNSGGNI
EDSDTGGGTSCTGNNATTANNPHSNVTQGSIGNPGQGSGTGLHPPVTSYPPTLGTSHSSHSVQSGLVRQSPA
RASVASQSSYCYSSRHSSLRMSTTGFVPCRRSSTSQISLRNLPSSIQSRLSMVNQMEPSGQSGLACVQHGLP
SSSSSSQSIPACKHHTLVGFLATEGGQSSATDAQPGNTLSPANNSHSRKAEVIYRVQIVDPSQILEGINLSK
RKELQWPDEGIRLKAGRNSWKDWSPQEGMEGHVIHRWVPCSRDPGTRSHIDKAVLLVQIDDKYVTVIETGVL.
ELGAEV
```

The disclosed NOV3 amino acid sequence has 1355 of 1446 amino acid residues (93%) identical to, and 1409 of 1446 amino acid residues (97%) similar to, the 1446 amino acid residue ptnr:SPTREMBL-ACC:Q9QYC1 protein from *Mus musculus* (Mouse) (PECANEX 1) (E = 0.0).

NOV3 is expressed in at least Pancreas, Parathyroid Gland, Thyroid, Mammary gland/Breast, Ovary, Placenta, Uterus, Colon, Liver, Bone Marrow, Lymphoid tissue, Spleen, Tonsils, Prostate, Testis, Brain, Lung, and Kidney . This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

In addition, NOV3 is predicted to be expressed in *Homo sapiens* heart, melanocyte, B-cells, larynx, skin, CNS, and multiple sclerosis lesions because of the expression pattern of the following sequences (which are publicly availabel ESTS for the sequence of the invention) AB018348, BE881203, BE867469, BE867415, AB007895, NM_014801, U74315, BE880986, W500099, AW250617, AA426168, AW246742, AA284182, W46420, H14491, Z44921, BE930588, AI922381, AI215559, AA923742, AA582883, BE797814,

N75143, BE049421, F07632, BE797239, AI168579, AV653955, BE065657, AL079849, and BE767656, closely related *Homo sapiens* mRNA for KIAA proteins, partial cds homolog.

NOV3 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 3C.

Table 3C. BLAST results for NOV3

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ref|XP_027243.1| (XM_027243)	hypothetical protein XP_027243 [Homo sapiens]	619	619/619 (100%)	619/619 (100%)	0.0
gi|15076843|gb|AAK82958.1|AF233450_1 (AF233450)	pecanex-like protein 1 [Homo sapiens]	2341	1372/1451 (94%)	1376/1451 (94%)	0.0
gi|6650377|gb|AAF21809.1|AF096286_1 (AF096286)	pecanex 1 [Mus musculus]	1446	1296/1446 (89%)	1344/1446 (92%)	0.0
gi|13171105|gb|AAK13590.1|AF154413_1 (AF154413)	pecanex [Takifugu rubripes]	1703	1079/1466 (73%)	1204/1466 (81%)	0.0
gi|7290294|gb|AAF45755.1| (AE003423)	pcx gene product [alt 1] [Drosophila melanogaster]	3437	320/554 (57%)	424/554 (75%)	0.0

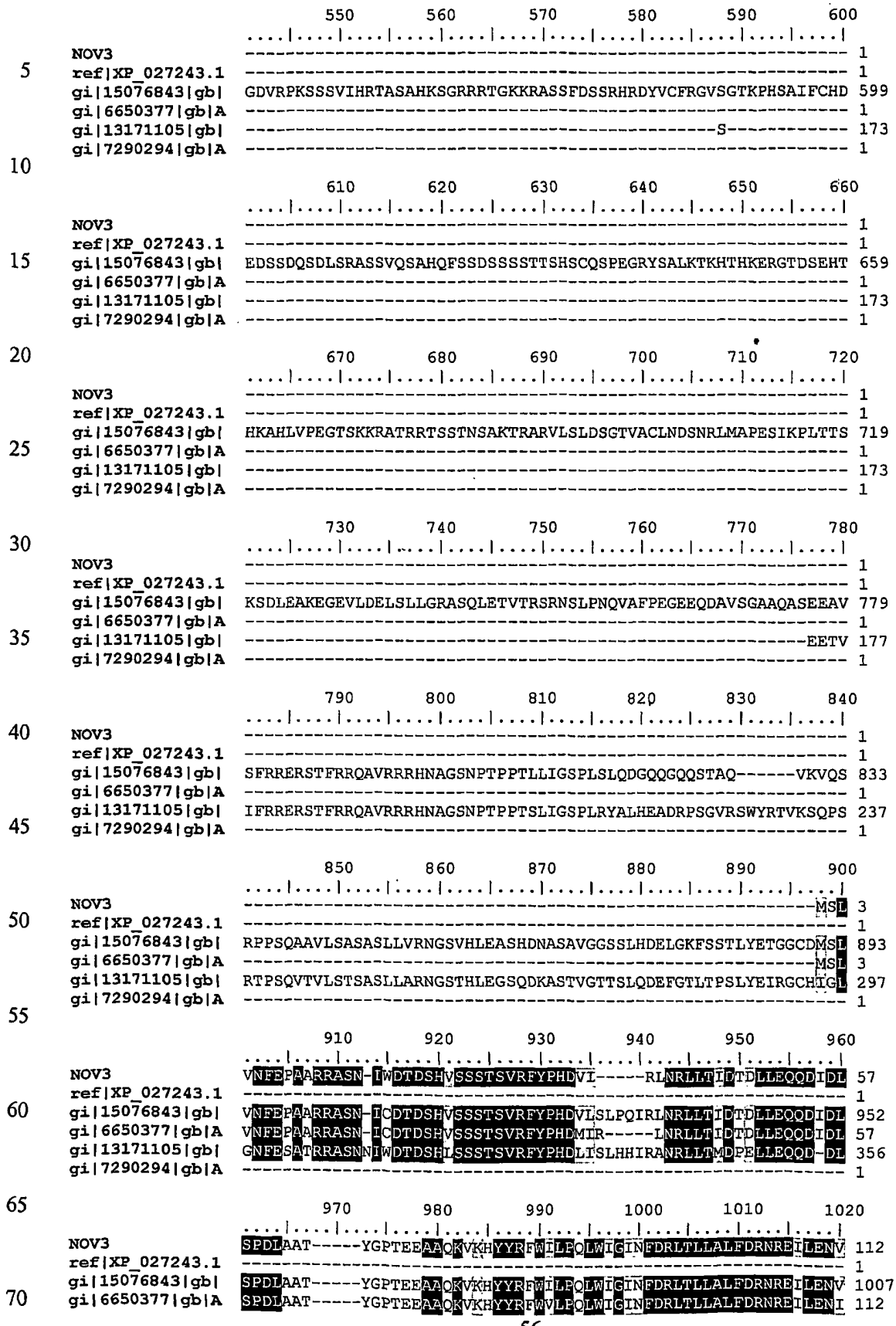
The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 3D.

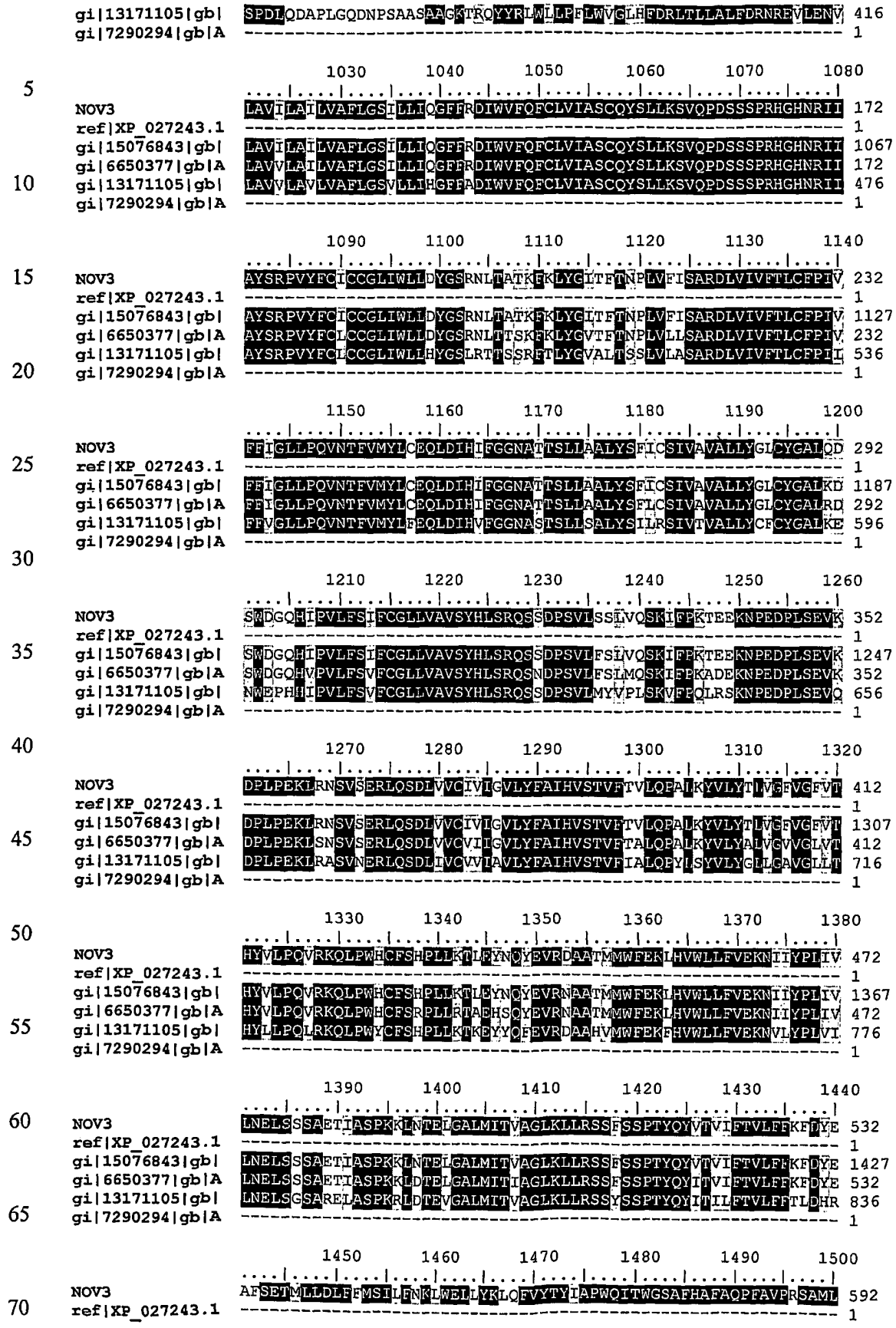
Table 3D. ClustalW Analysis of NOV3

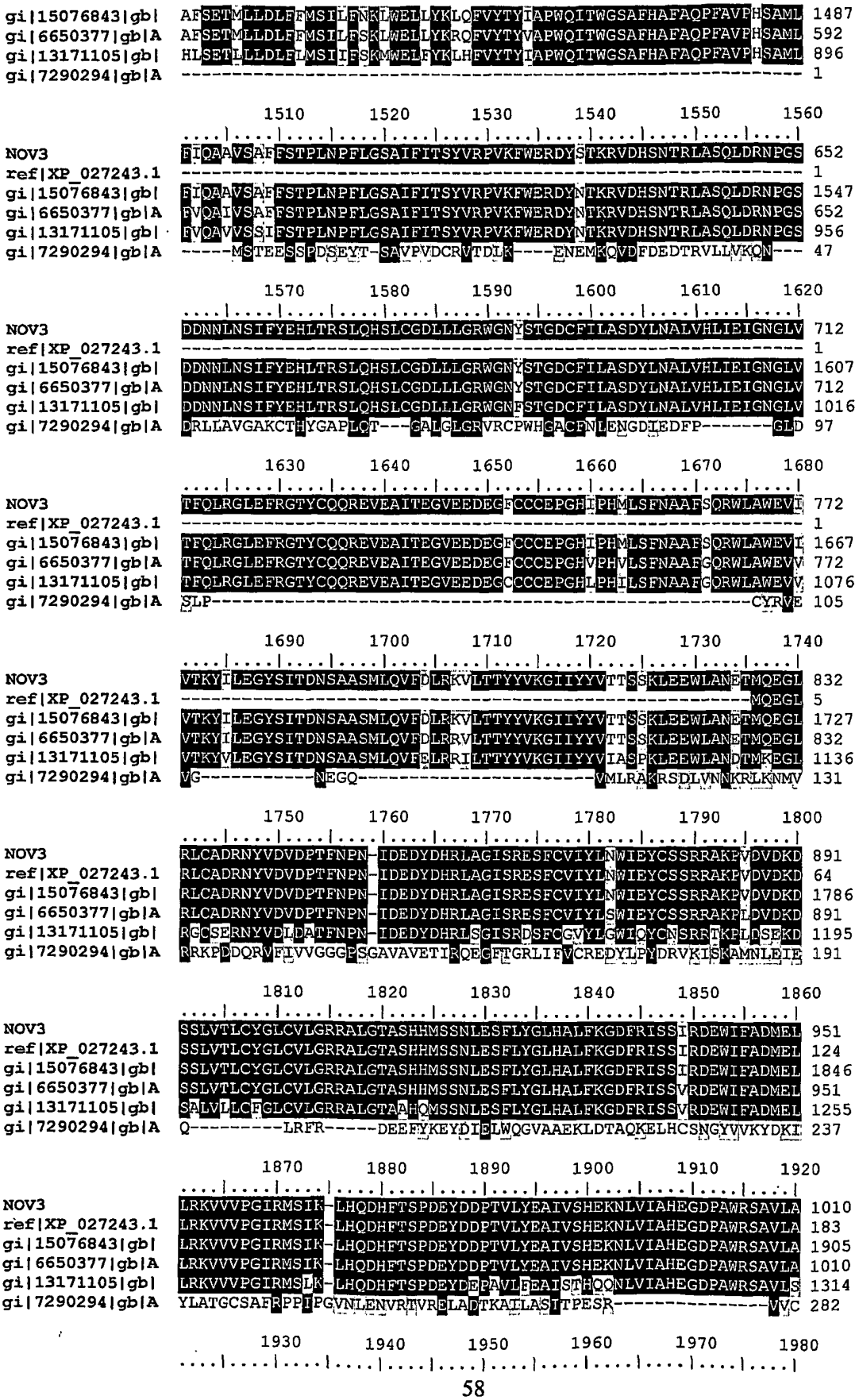
1) NOV3 (SEQ ID NO:12)
2) ref|XP_027243.1| (XM_027243) hypothetical protein XP_027243 [Homo sapiens] (SEQ ID NO:42)
3) gi|15076843|gb|AAK82958.1|AF233450_1 (AF233450) pecanex-like protein 1 [Homo sapiens] (SEQ ID NO:43)
4) gi|6650377|gb|AAF21809.1|AF096286_1 (AF096286) pecanex 1 [Mus musculus] (SEQ ID NO:44)
5) gi|13171105|gb|AAK13590.1|AF154413_1 (AF154413) pecanex [Takifugu rubripes] (SEQ ID NO:45)
6) gi|7290294|gb|AAF45755.1| (AE003423) pcx gene product [alt 1] [Drosophila melanogaster] (SEQ ID NO:46)

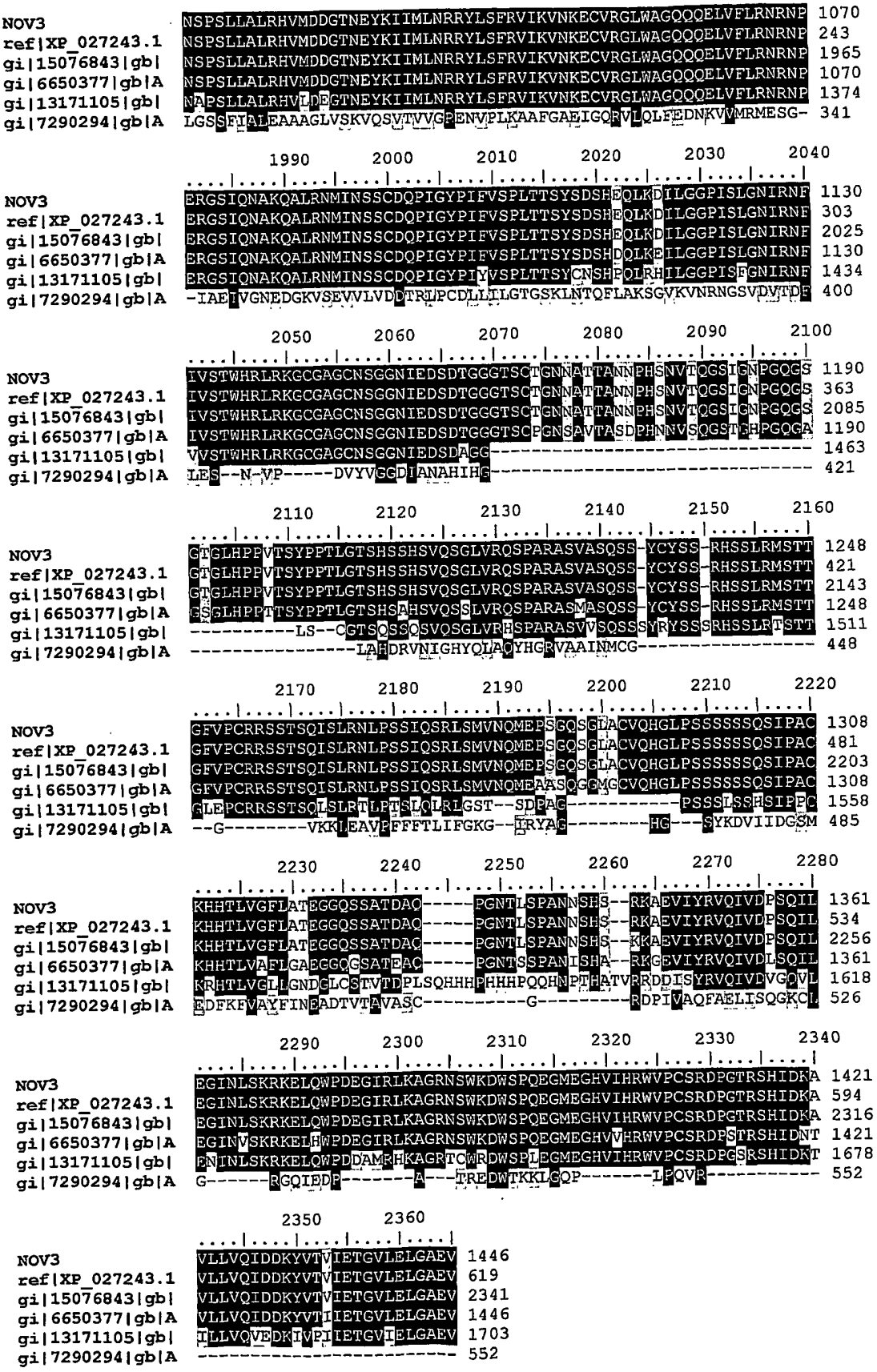
```
                          10        20        30        40        50        60
                  ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3              ------------------------------------------------------------ 1
ref|XP_027243.1   ------------------------------------------------------------ 1
gi|15076843|gb|   MGSQTLQILRQGVWAALSGGWYYDPHQATFVNALHLYLWLFLLGLPFTLYMALPSTMIIV 60
gi|6650377|gb|A   ------------------------------------------------------------ 1
gi|13171105|gb|   MGSQTLQILRQGVWASVTGGWYYDPDQNTFVNALHLYIWLFLLCFPFTLYMALQPSMVIV 60
gi|7290294|gb|A   ------------------------------------------------------------ 1

                          70        80        90        100       110       120
```

```
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     AVYCPVIAAVFIVLKMVNYRLHRALDAGEVVDRTANEFTDQR-TKAEQGNCSTRRKDSNG 119
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     GIYCGVIAAMFLLLKTVNYRLHHALDEGEVVEHQTRESKGSRGGTGGANDPVTRREDSNG 120
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            130       140       150       160       170       180
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     PSDPGGGIEMSEFIREATPPVGCSSRNSYAGLDPSNQIGSGSSRLGTAATIKGDTDTAKT 179
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     LGDPGGGIEMADFIRQETPPVDCSSRNSYVG---------------------------- 151
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            190       200       210       220       230       240
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     SDDISLSLGQSSSLCKEGSEEQDLAADRKLFRLVSNDSFISIQPSLSSCGQDLPRDFSDK 239
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     ------------------------------------------------------------ 151
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            250       260       270       280       290       300
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     VNLPSHNHHHHVDQSLSSACDTEVASLVPLHSHSYRKDHRPRGVPRTSSSAVAFPDTSLN 299
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     ------------------------------------------------------------ 151
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            310       320       330       340       350       360
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     DFPLYQQRRGLDPVSELESSKPLSGSKESLVENSGLSGEFQLAGDLKINTSQPPTKSGKS 359
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     ------------------------------------------------------------ 151
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            370       380       390       400       410       420
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     KPLKAEKSMDSLRSLSTRSSGSTESYCSGTDRDTNSTVSSYKSEQTSSTHIESILSEHEE 419
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     ---------------------------------------------------------MDL 154
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            430       440       450       460       470       480
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     SPKAGTKSGRKKECCAGPEEKNSCASDKRTSSEKIAMEASTNSGVHEAKDPTPSDEMHNQ 479
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     NQRMSSTHGRTTVAKAPG---------------------------------------- 172
gi|7290294|gb|A     ------------------------------------------------------------ 1

                            490       500       510       520       530       540
                    ....|....|....|....|....|....|....|....|....|....|....|....|
NOV3                ------------------------------------------------------------ 1
ref|XP_027243.1     ------------------------------------------------------------ 1
gi|15076843|gb|     RGLSTSASEEANKNPHANEFTSQGDRPPGNTAENKEEKSDKSAVSVDSKVRKDVGGKQKE 539
gi|6650377|gb|A     ------------------------------------------------------------ 1
gi|13171105|gb|     ------------------------------------------------------------ 172
gi|7290294|gb|A     ------------------------------------------------------------ 1
```


550 560 570 580 590 600
NOV3 ---------- 1
ref|XP_027243.1 ---------- 1
gi|15076843|gb| GDVRPKSSSVIHRTASAHKSGRRRTGKKRASSFDSSRHRDYVCFRGVSGTKPHSAIFCHD 599
gi|6650377|gb|A ---------- 1
gi|13171105|gb| ----------S---------- 173
gi|7290294|gb|A ---------- 1
610 620 630 640 650 660
NOV3 ---------- 1
ref|XP_027243.1 ---------- 1
gi|15076843|gb| EDSSDQSDLSRASSVQSAHQFSSDSSSSTTSHSCQSPEGRYSALKTKHTHKERGTDSEHT 659
gi|6650377|gb|A ---------- 1
gi|13171105|gb| ---------- 173
gi|7290294|gb|A ---------- 1
670 680 690 700 710 720
NOV3 ---------- 1
ref|XP_027243.1 ---------- 1
gi|15076843|gb| HKAHLVPEGTSKKRATRRTSSTNSAKTRARVLSLDSGTVACLNDSNRLMAPESIKPLTTS 719
gi|6650377|gb|A ---------- 1
gi|13171105|gb| ---------- 173
gi|7290294|gb|A ---------- 1
730 740 750 760 770 780
NOV3 ---------- 1
ref|XP_027243.1 ---------- 1
gi|15076843|gb| KSDLEAKEGEVLDELSLLGRASQLETVTRSRNSLPNQVAFPEGEEQDAVSGAAQASEEAV 779
gi|6650377|gb|A ---------- 1
gi|13171105|gb| ----------EETV 177
gi|7290294|gb|A ---------- 1
790 800 810 820 830 840
NOV3 ---------- 1
ref|XP_027243.1 ---------- 1
gi|15076843|gb| SFRRERSTFRRQAVRRRHNAGSNPTPPTLLIGSPLSLQDGQQGQQSTAQ------VKVQS 833
gi|6650377|gb|A ---------- 1
gi|13171105|gb| IFRRERSTFRRQAVRRRHNAGSNPTPPTSLIGSPLRYALHEADRPSGVRSWYRTVKSQPS 237
gi|7290294|gb|A ---------- 1
850 860 870 880 890 900
NOV3 ----------MSL 3
ref|XP_027243.1 ---------- 1
gi|15076843|gb| RPPSQAAVLSASASLLVRNGSVHLEASHDNASAVGGSSLHDELGKFSSTLYETGGCDMSL 893
gi|6650377|gb|A ----------MSL 3
gi|13171105|gb| RTPSQVTVLSTSASLLARNGSTHLEGSQDKASTVGTTSLQDEFGTLTPSLYEIRGCHIGL 297
gi|7290294|gb|A ---------- 1
910 920 930 940 950 960
NOV3 VNFEPAARRASN-IWDTDSHVSSSTSVRFYPHDVI-----RLNRLLTIDTDLLEQQDIDL 57
ref|XP_027243.1 ---------- 1
gi|15076843|gb| VNFEPAARRASN-ICDTDSHVSSSTSVRFYPHDVLSLPQIRLNRLLTIDTDLLEQQDIDL 952
gi|6650377|gb|A VNFEPAARRASN-ICDTDSHVSSSTSVRFYPHDMIR-----LNRLLTIDTDLLEQQDIDL 57
gi|13171105|gb| GNFESATRRASNNIWDTDSHLSSSTSVRFYPHDLISLHHIRANRLLTMDPELLEQQD-DL 356
gi|7290294|gb|A ---------- 1
970 980 990 1000 1010 1020
NOV3 SPDLAAT-----YGPTEEAAQKVKHYYRFWILPQLWIGINFDRLTLLALFDRNREILENV 112
ref|XP_027243.1 ---------- 1
gi|15076843|gb| SPDLAAT-----YGPTEEAAQKVKHYYRFWILPQLWIGINFDRLTLLALFDRNREILENV 1007
gi|6650377|gb|A SPDLAAT-----YGPTEEAAQKVKHYYRFWVLPQLWIGINFDRLTLLALFDRNREILENI 112


gi|13171105|gb| SPDLQDAPLGQDNPSAASAAGKTRQYYRLWLLPFLWVGLHFDRLTLLALFDRNREVLENV 416
gi|7290294|gb|A ---------- 1
1030 1040 1050 1060 1070 1080
NOV3 LAVILAILVAFLGSILLIQGFFRDIWVFQFCLVIASCQYSLLKSVQPDSSSPRHGHNRII 172
ref|XP_027243.1 ---------- 1
gi|15076843|gb| LAVILAILVAFLGSILLIQGFFRDIWVFQFCLVIASCQYSLLKSVQPDSSSPRHGHNRII 1067
gi|6650377|gb|A LAVVLAILVAFLGSILLIQGFFRDIWVFQFCLVIASCQYSLLKSVQPDSSSPRHGHNRII 172
gi|13171105|gb| LAVVLAVLVAFLGSVLLIHGFFADIWVFQFCLVIASCQYSLLKSVQPDSSSPRHGHNRII 476
gi|7290294|gb|A ---------- 1
1090 1100 1110 1120 1130 1140
NOV3 AYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGLTFTNPLVFISARDLVIVFTLCFPIV 232
ref|XP_027243.1 ---------- 1
gi|15076843|gb| AYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGLTFTNPLVFISARDLVIVFTLCFPIV 1127
gi|6650377|gb|A AYSRPVYFCLCCGLIWLLDYGSRNLTTSKFKLYGVTFTNPLVLLSARDLVIVFTLCFPIV 232
gi|13171105|gb| AYSRPVYFCLCCGLIWLLHYGSLRTTSSRFTLYGVALTSSLVLASARDLVIVFTLCFPII 536
gi|7290294|gb|A ---------- 1
1150 1160 1170 1180 1190 1200
NOV3 FFIGLLPQVNTFVMYLCEQLDIHIFGGNATTSLLAALYSFICSIVAVALLYGLCYGALQD 292
ref|XP_027243.1 ---------- 1
gi|15076843|gb| FFIGLLPQVNTFVMYLCEQLDIHIFGGNATTSLLAALYSFICSIVAVALLYGLCYGALKD 1187
gi|6650377|gb|A FFIGLLPQVNTFVMYLCEQLDIHIFGGNATTSLLAALYSFLCSIVAVALLYGLCYGALRD 292
gi|13171105|gb| FFVGLLPQVNTFVMYLFEQLDIHVFGGNASTSLLSALYSILRSIVTVALLYCFCYGALKE 596
gi|7290294|gb|A ---------- 1
1210 1220 1230 1240 1250 1260
NOV3 SWDGQHIPVLFSIFCGLLVAVSYHLSRQSSDPSVLSSLVQSKIFFKTEEKNPEDPLSEVK 352
ref|XP_027243.1 ---------- 1
gi|15076843|gb| SWDGQHIPVLFSIFCGLLVAVSYHLSRQSSDPSVLFSLVQSKIFFKTEEKNPEDPLSEVK 1247
gi|6650377|gb|A SWDGQHVPVLFSVFCGLLVAVSYHLSRQSNDPSVLFSLMQSKIFFKADEKNPEDPLSEVK 352
gi|13171105|gb| NWEPHHIPVLFSVFCGLLVAVSYHLSRQSSDPSVLMYVPLSKVFFQLRSKNPEDPLSEVQ 656
gi|7290294|gb|A ---------- 1
1270 1280 1290 1300 1310 1320
NOV3 DPLPEKLRNSVSERLQSDLVVCIVIGVLYFAIHVSTVFTVLQPAIKYVLYTLVGFVGFVT 412
ref|XP_027243.1 ---------- 1
gi|15076843|gb| DPLPEKLRNSVSERLQSDLVVCIVIGVLYFAIHVSTVFTVLQPALKYVLYTLVGFVGFVT 1307
gi|6650377|gb|A DPLPEKLSNSVSERLQSDLVVCVIIGVLYFAIHVSTVFTALQPALKYVLYALVGVVGLVT 412
gi|13171105|gb| DPLPEKLRASVNERLQSDLIVCVVIAVLYFAIHVSTVFIALQPYLSYVLYGLLGAVGLLT 716
gi|7290294|gb|A ---------- 1
1330 1340 1350 1360 1370 1380
NOV3 HYVLPQVRKQLPWHCFSHPLLKTLEYNQYEVRDAATMMWFEKLHVWLLFVEKNIIYPIIV 472
ref|XP_027243.1 ---------- 1
gi|15076843|gb| HYVLPQVRKQLPWHCFSHPLLKTLEYNQYEVRNAATMMWFEKLHVWLLFVEKNIIYPLIV 1367
gi|6650377|gb|A HYVLPQVRKQLPWHCFSRPLLRTADHSQYEVRNAATMMWFEKLHVWLLFVEKNIIYPLIV 472
gi|13171105|gb| HYLLPQLRKQLPWYCFSHPLLKTKEYYQFEVRDAAHVMWFEKFHVWLLFVEKNVLYPLVI 776
gi|7290294|gb|A ---------- 1
1390 1400 1410 1420 1430 1440
NOV3 LNELSSSAETIASPKKLNTELGALMITVAGLKLLRSSFSSPTYQYVTVIFTVLFFKFDYE 532
ref|XP_027243.1 ---------- 1
gi|15076843|gb| LNELSSSAETIASPKKLNTELGALMITVAGLKLLRSSFSSPTYQYVTVIFTVLFFKFDYE 1427
gi|6650377|gb|A LNELSSSAETIASPKKLDTELGALMITIAGLKLLRSSFSSPTYQYITVIFTVLFFKFDYE 532
gi|13171105|gb| LNELSGSARELASPKRLDTEVGALMITVAGLKLLRSSYSSPTYQYITILFTVLFFTLDHR 836
gi|7290294|gb|A ---------- 1
1450 1460 1470 1480 1490 1500
NOV3 AFSETMLLDLFFMSILFNKLWELLYKLQFVYTYIAPWQITWGSAFHAFAQPFAVPRSAML 592
ref|XP_027243.1 ---------- 1


gi|15076843|gb| AFSETMLLDLFFMSILFNKLWELLYKLQFVYTYIAPWQITWGSAFHAFAQPFAVPHSAML 1487
gi|6650377|gb|A AFSETMLLDLFFMSILFSKLWELLYKRQFVYTYVAPWQITWGSAFHAFAQPFAVPHSAML 592
gi|13171105|gb| HLSETLLLDLFLMSIIFSKMWELFYKLHFVYTYIAPWQITWGSAFHAFAQPFAVPHSAML 896
gi|7290294|gb|A ---------- 1
1510 1520 1530 1540 1550 1560
NOV3 FIQAAVSAFFSTPLNPFLGSAIFITSYVRPVKFWERDYSTKRVDHSNTRLASQLDRNPGS 652
ref|XP_027243.1 ---------- 1
gi|15076843|gb| FIQAAVSAFFSTPLNPFLGSAIFITSYVRPVKFWERDYNTKRVDHSNTRLASQLDRNPGS 1547
gi|6650377|gb|A FVQAIVSAFFSTPLNPFLGSAIFITSYVRPVKFWERDYNTKRVDHSNTRLASQLDRNPGS 652
gi|13171105|gb| FVQAVVSSIFSTPLNPFLGSAIFITSYVRPVKFWERDYNTKRVDHSNTRLASQLDRNPGS 956
gi|7290294|gb|A -----MSTEESSPDSEYT-SAVPVDCRVTDLK----ENEMKQVDFDEDTRVLLVKQN--- 47
1570 1580 1590 1600 1610 1620
NOV3 DDNNLNSIFYEHLTRSLQHSLCGDLLLGRWGNYSTGDCFILASDYLNALVHLIEIGNGLV 712
ref|XP_027243.1 ---------- 1
gi|15076843|gb| DDNNLNSIFYEHLTRSLQHSLCGDLLLGRWGNYSTGDCFILASDYLNALVHLIEIGNGLV 1607
gi|6650377|gb|A DDNNLNSIFYEHLTRSLQHSLCGDLLLGRWGNYSTGDCFILASDYLNALVHLIEIGNGLV 712
gi|13171105|gb| DDNNLNSIFYEHLTRSLQHSLCGDLLLGRWGNFSTGDCFILASDYLNALVHLIEIGNGLV 1016
gi|7290294|gb|A DRLLAVGAKCTHYGAPLQT---GALGLGRVRCPWHGACFNLENGDIEDFP-------GLD 97
1630 1640 1650 1660 1670 1680
NOV3 TFQLRGLEFRGTYCQQREVEAITEGVEEDEGFCCCEPGHIPHMLSFNAAFSQRWLAWEVI 772
ref|XP_027243.1 ---------- 1
gi|15076843|gb| TFQLRGLEFRGTYCQQREVEAITEGVEEDEGFCCCEPGHIPHMLSFNAAFSQRWLAWEVI 1667
gi|6650377|gb|A TFQLRGLEFRGTYCQQREVEAITEGVEEDEGFCCCEPGHVPHVLSFNAAFGQRWLAWEVV 772
gi|13171105|gb| TFQLRGLEFRGTYCQQREVEAITEGVEEDEGCCCCEPGHLPHILSFNAAFGQRWLAWEVV 1076
gi|7290294|gb|A SLP----------CYRVE 105
1690 1700 1710 1720 1730 1740
NOV3 VTKYILEGYSITDNSAASMLQVFDLRKVLTTYYVKGIIYYVTTSSKLEEWLANETMQEGL 832
ref|XP_027243.1 ----------MQEGL 5
gi|15076843|gb| VTKYILEGYSITDNSAASMLQVFDLRKVLTTYYVKGIIYYVTTSSKLEEWLANETMQEGL 1727
gi|6650377|gb|A VTKYILEGYSITDNSAASMLQVFDLRRVLTTYYVKGIIYYVTTSSKLEEWLANETMQEGL 832
gi|13171105|gb| VTKYVLEGYSITDNSAASMLQVFELRRILTTYYVKGIIYYVIASPKLEEWLANDTMKEGL 1136
gi|7290294|gb|A VG----------NEGQ----------VMLRAKRSDLVNNKRLKNMV 131
1750 1760 1770 1780 1790 1800
NOV3 RLCADRNYVDVDPTFNPN-IDEDYDHRLAGISRESFCVIYLNWIEYCSSRRAKPVDVDKD 891
ref|XP_027243.1 RLCADRNYVDVDPTFNPN-IDEDYDHRLAGISRESFCVIYLNWIEYCSSRRAKPVDVDKD 64
gi|15076843|gb| RLCADRNYVDVDPTFNPN-IDEDYDHRLAGISRESFCVIYLNWIEYCSSRRAKPVDVDKD 1786
gi|6650377|gb|A RLCADRNYVDVDPTFNPN-IDEDYDHRLAGISRESFCVIYLSWIEYCSSRRAKPLDVDKD 891
gi|13171105|gb| RCCSERNYVDLDATFNPN-IDEDYDHRLSGISRDSFCGVYLGWIQYCNSRRTKPLDSEKD 1195
gi|7290294|gb|A RRKPDDQRVFIVVGGGPSGAVAVETIRQEGFTGRLIFVCREDYLPYDRVKISKAMNLEIE 191
1810 1820 1830 1840 1850 1860
NOV3 SSLVTLCYGLCVLGRRALGTASHHMSSNLESFLYGLHALFKGDFRISSIRDEWIFADMEL 951
ref|XP_027243.1 SSLVTLCYGLCVLGRRALGTASHHMSSNLESFLYGLHALFKGDFRISSIRDEWIFADMEL 124
gi|15076843|gb| SSLVTLCYGLCVLGRRALGTASHHMSSNLESFLYGLHALFKGDFRISSIRDEWIFADMEL 1846
gi|6650377|gb|A SSLVTLCYGLCVLGRRALGTASHHMSSNLESFLYGLHALFKGDFRISSVRDEWIFADMEL 951
gi|13171105|gb| SALVLLCFGLCVLGRRALGTAAHQMSSNLESFLYGLHALFKGDFRISSVRDEWIFADMEL 1255
gi|7290294|gb|A Q---------LRFR-----DEEFYKEYDIELWQGVAAEKLDTAQKELHCSNGYVVKYDKI 237
1870 1880 1890 1900 1910 1920
NOV3 LRKVVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAWRSAVLA 1010
ref|XP_027243.1 LRKVVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAWRSAVLA 183
gi|15076843|gb| LRKVVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAWRSAVLA 1905
gi|6650377|gb|A LRKVVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAWRSAVLA 1010
gi|13171105|gb| LRKVVVPGIRMSLK-LHQDHFTSPDEYDEPAVLEEAISTHQQNLVIAHEGDPAWRSAVLS 1314
gi|7290294|gb|A YLATGCSAFRPPIPGVNLENVRTVRELADTKAILASITPESR----------VVC 282
1930 1940 1950 1960 1970 1980


NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A
1990 2000 2010 2020 2030 2040
2050 2060 2070 2080 2090 2100
2110 2120 2130 2140 2150 2160
2170 2180 2190 2200 2210 2220
2230 2240 2250 2260 2270 2280
2290 2300 2310 2320 2330 2340
2350 2360

Pecanex gene was originally discovered in *Drosophila*, encoding a large, membrane-spanning protein. The mouse homolog was recently reported. In the absence of maternal expression of the pecanex gene, the embryo develops severe hyperneuralization similar to that characteristic of Notch mutant embryos. Early gastrula embryos, lacking both maternally and zygotically expressed activity of the neurogenic pecanex locus, are shown to contain a greater than wild-type number of stably determined neural precursor cells which can differentiate into neurons in culture. Therefore it is anticipated that this novel human pecanex will be involved in neuronal differentiation, maintenance of neuronal precursors and neurological diseases.

The disclosed NOV3 nucleic acid of the invention encoding a Human homolog of the *Drosophila* pecanex protein includes the nucleic acid whose sequence is provided in Table 3A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 3A while still encoding a protein that maintains its Human homolog of the *Drosophila* pecanex activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 1 percent of the bases may be so changed.

The disclosed NOV3 protein of the invention includes the Human homolog of the *Drosophila* pecanex protein whose sequence is provided in Table 3B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 3B while still encoding a protein that maintains its Human homolog of the *Drosophila* pecanex activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 7 percent of the residues may be so changed.

The NOV3 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer,trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, cardiomyopathy, atherosclerosis, hypertension, congenital

heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, multiple sclerosis, scleroderma, obesity, endometriosis, fertility, hypercoagulation, autoimmume disease, allergies, immunodeficiencies, transplantation, hemophilia, idiopathic thrombocytopenic purpura, graft versus host disease, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, systemic lupus erythematosus, asthma, emphysema, ARDS, laryngitis, psoriasis, actinic keratosis, acne, hair growth/loss, allopecia, pigmentation disorders, endocrine disorders, diabetes, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, Lesch-Nyhan syndrome, and a variety of kidney diseases and/or other pathologies and disorders.

NOV3 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV3 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV3 epitope is from about amino acids 20 to 50. In another embodiment, a NOV3 epitope is from about amino acids 180 to 200. In additional embodiments, NOV3 epitopes are from about amino acids 360 to 400, from about 450 to 500, from about amino acids 600 to 680, from about amino acids 720 to 780, from about amino acids 800 to 860, from about amino acids 950 to 1000, from about amino acids 1050 to 1100, from about amino acids 1150 to 1320, and from about amino acids 1350 to 1420. These novel proteins can be used in assay systems for functional analysis of various human disorders, which are useful in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV4

A disclosed NOV4 nucleic acid of 1500 nucleotides (also referred to as SC140515441_A) encoding a novel Aurora-related kinase 1-like protein is shown in Table 4A. An open reading frame was identified beginning with a ATG initiation codon at nucleotides 182-184 and ending with a TAG codon at nucleotides 1391-1393. The start and stop codons are in bold letters, and the 5' and 3' untranslated regions are underlined.

Table 4A. NOV4 Nucleotide Sequence (SEQ ID NO:13)

TCATCTTAAATTTTTTTAGCTGATATAGTTGTAATTTCTTAACCTAGCTCATCTCTAGAGGATATGTAAAA
ACATAAAACACCTCAATTACTTGTGAATTATAGAGGTGTATCAGTTGGTTTAAAAGTGCTTTTATTGGGCT
GAGCTCTTGGAAGACTCAGGTCCTTGGGTCATAGGCATCATGGACCAATCTGAAGAAAACTGCATTTCAGG
GCCTGTTGAGGCTAAAACTCCAGTTGGAGGTCCAGAACATGTTCTCGTGACTCAGCAATTTCCTTGTCAGA
ATCCATTACCTGCAAATAGTGGCCAGGCTCAGTGGGTCTTGTGTCCTTCAAATTCTTCGCAGCGTGTTCCT
TTGCAAGCACAAAAGCTTGTCTCCAGTCACAAGCCAGTTCAGAATCAGAAGCAGAAGCAATTGCAGGCAAC
CAGTGTACCTCATCCTGCCTCCAGGCCACTGAATAACACCCAAAACAGCAAGCAGTCCCCGCTGTCGGCAC
CTGAAAATAATCCTGAGGAGGAACTGGCATCAAAACAGAAAAATGAAGAATCAAAAAAGAGGCAATGGGCT
TTGGAAGACCTTGAAATTGGTCGCCCTCCGGGTAAAGGAAAGTTTGGTAATGTTTATTTGGCAAGAGAAAA
ACAAAGCAAGTTTATTCTGGCTCTTAGGGTGTTATTTAAAGCTCAGCTGGAGAAAGCAGGAGTGGAGCATC
AACTCAGAAGAGAAGTAGAAATACAGTCCCACCTCCAACATCCTAATATAATCAGACTGTATGGTTATTTC
CATGATGCCACCAGAGTCTACCTAATTCTGGAATATACACCACTTGAAACAGTCAATACAGAACTTCAGAA
ACTTTCAAAGTTTGATGAGCAGAGAACTGCTACTTATATCACAGAATTGGCAAGTGCCCTGTCTTACTGTC
ATTCAAAAACAGTTATTCATAGAGACATTAAGCCAGAGAACTTACTTCTTGGATCAGCTGGAGAGCTTGAA
ATTGCAAATTTTGGGTGGTCAGAACATGCTCCATCTTCCAGGAGGACCACTCTCTGTGGCACCCTGGACTA
CCTGCCCCCCGAAATGATTGAAGGTCGGATGCATGATGAGAAGGTGGATCTCTGGAGCCTTGGAGTTCTTT
GCTGTGAATTTTTAGTTGGGAAGCCTCCTTTTGAGGCAAATACATACCAAGAGACCTACAAAAGAATATCA
CGGGTTGAGTTCACATTCCCTGACTTTGTAACAGAGGGAGCCAGGGACCTCATTTCAAGACTGTTGAAGCA
TGTTCCCAGCCAGAGGCCAATGCTCAGAGAAGTACTTGAATACCCCTGGATCACAGCAAATTCATCAAAAC
CATCAAATTGCCAAAACAAAGAATCAACTAGCAAGTATTCTTAGGAATCGTGCAGGGGGAGAAATCCTTGA
GCCAGGGCTGCTGTATAACCTCTCAGGAACATGCTACCAAAATTTATTTTACCATTGACTGCTGCCCTCAA
TCTAGAACA

The disclosed NOV4 nucleic acid sequence maps to chromosome 1 and has 1152 of 1212 bases (95%) identical to a gb:GENBANK-ID:AF008551|acc:AF008551 mRNA from *Homo sapiens* (*Homo sapiens* aurora-related kinase 1 (ARK1) mRNA, complete cds ($E = 1.8e^{-243}$).

A disclosed NOV4 protein (SEQ ID NO:14) encoded by SEQ ID NO:13 has 403 amino acid residues, and is presented using the one-letter code in Table 4B. Signal P, Psort and/or Hydropathy results predict that NOV4 does not have a signal peptide, and is likely to be localized to the cytoplasm with a certainty of 0.4500. In other embodiments NOV4 is also likely to be localized microbody (peroxisome) with a certainty of 0.3000, to the mitochondrial membrane space with a certainty of 0.1000, or to the lysosome(lumen) with a certainty of 0.1000.

Table 4B. Encoded NOV4 protein sequence (SEQ ID NO:14).

MDQSEENCISGPVEAKTPVGGPEHVLVTQQFPCQNPLPANSGQAQWVLCPSNSSQRVPLQAQKLVSSHKPV
QNQKQKQLQATSVPHPASRPLNNTQNSKQSPLSAPENNPEEELASKQKNEESKKRQWALEDLEIGRPPGKG
KFGNVYLAREKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLQHPNIIRLYGYFHDATRVYLILEYT
PLETVNTELQKLSKFDEQRTATYITELASALSYCHSKTVIHRDIKPENLLLGSAGELKIANFGWSEHAPSS
RRTTLCGTLDYLPPEMIEGRMHDEKVDLWSLGVLCCEFLVGKPPFEANTYQETYKRISRVEFTFPDFVTEG
ARDLISRLLKHVPSQRPMLREVLEYPWITANSSKPSNCQNKESTSKYS

The disclosed NOV4 amino acid has 69 of 403 amino acid residues (91%) identical to, and 381 of 403 amino acid residues (94%) similar to, the 403 amino acid residue

ptnr:SPTREMBL-ACC:O60445 protein from *Homo sapiens* (Human) (Aurora-Related Kinase 1 (E= $1.7e^{-198}$).

NOV4 is expressed in at least Adrenal Gland/Suprarenal gland, Amygdala, Bone Marrow, Brain, Cervix, Colon, Coronary Artery, Epidermis, Heart, Kidney, Liver, Lung, Lymphoid tissue, Mammary gland/Breast, Ovary, Peripheral Blood, Placenta, Prostate, Testis, Thalamus, Tonsils, Uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention.

In addition, NOV4 is predicted to be expressed in colon because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF008551|acc:AF008551) a closely related aurora-related kinase 1 (ARK1) mRNA, complete cds homolog in species *Homo sapiens*.

NOV4 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 4C.

Table 4C. BLAST results for NOV4

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|12654873|gb|AAH01280.1|AAH01280 (BC001280)	serine/threonine kinase 15 [Homo sapiens]	403	370/403 (91%)	381/403 (93%)	0.0
gi|13653970|ref|XP_009546.3| (XM_009546)	serine/threonine kinase 15 [Homo sapiens]	403	369/403 (91%)	381/403 (93%)	0.0
gi|4507275|ref|NP_003591.1| (NM_003600)	serine/threonine kinase 15; Serine/threonine protein kinase 15 [Homo sapiens]	403	369/403 (91%)	380/403 (93%)	0.0
gi|7446411|pir||JC5974	aurora-related kinase 1 (EC 2.7.-.-) - human	403	367/403 (91%)	379/403 (93%)	0.0
gi|4507279|ref|NP_003149.1| (NM_003158)	serine/threonine kinase 6; Serine/threonine protein kinase-6; serine/threonine kinase 6 (aurora/IPL1-like) [Homo sapiens]	402	342/403 (84%)	360/403 (88%)	0.0

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 4D.

Table 4D. ClustalW Analysis of NOV4

1) NOV4 (SEQ ID NO:14)
2) gi|12654873|gb|AAH01280.1|AAH01280 (BC001280) serine/threonine kinase 15 [Homo sapiens] (SEQ ID NO:47)
3) gi|13653970|ref|XP_009546.3| (XM_009546) serine/threonine kinase 15 [Homo sapiens] (SEQ ID NO:48)
4) gi|4507275|ref|NP_003591.1| (NM_003600) serine/threonine kinase 15; Serine/threonine protein kinase 15 [Homo sapiens] (SEQ ID NO:49)
5) gi|7446411|pir||JC5974 aurora-related kinase 1 (EC 2.7.-.-) - human (SEQ ID NO:50)
6) gi|4507279|ref|NP_003149.1| (NM_003158) serine/threonine kinase 6; Serine/threonine protein kinase-6; serine/threonine kinase 6 (aurora/IPL1-like) [Homo sapiens] (SEQ ID NO:51)

```
                    10        20        30        40        50
                    ....|....|....|....|....|....|....|....|....|....|
NOV4                MDQSEENCISGPVEAKTPVGGPEHVLVTQQFPCQNPLPANSGQAQWVLCP
gi|12654873|        MDRSKENCISGPVKATAPVGGPKRVLVTQQFPCQNPLPVNSGQAQRVLCP
gi|13653970|        MDRSKENCISGPVKATAPVGGPKRVLVTQQFPCQNPLPVNSGQAQRVLCP
gi|4507275|         MDRSKENCISGPVKATAPVGGPKRVLVTQQIPCQNPLPVNSGQAQRVLCP
gi|7446411|         MDRSKENCISGPVKATAPVGGPKRVLVTQQFPCQNPLPVNSGQAQRVLCP
gi|4507279|         MDRSKENCISGPVKATAPVGGPKRVLVTQQFPCQNPLPVNSGQAQRVLCP

                    60        70        80        90        100
                    ....|....|....|....|....|....|....|....|....|....|
NOV4                SNSSQRVPLQAQKLVSSHKPVQNQKQKQLQATSVPHPASRPLNNTQNSKQ
gi|12654873|        SNSSQRVPLQAQKLVSSHKPVQNQKQKQLQATSVPHPVSRPLNNTQKSKQ
gi|13653970|        SNSSQRIPLQAQKLVSSHKPVQNQKQKQLQATSVPHPVSRPLNNTQKSKQ
gi|4507275|         SNSSQRVPLQAQKLVSSHKPVQNQKQKQLQATSVPHPVSRPLNNTQKSKQ
gi|7446411|         SNSSQRIPLQAQKLVSSHKPVQNQKQKQLQQTSVPHPVSRPLNNTQKSKQ
gi|4507279|         SNSSQRVPLQAQKLVSSHKPVQNQKQKQLQATSVPHPVSRPLNNTQKSKQ

                    110       120       130       140       150
                    ....|....|....|....|....|....|....|....|....|....|
NOV4                SPLSAPENNPEEELASKQKNEESKKRQWALEDLEIGRPPGKGKFGNVYLA
gi|12654873|        PLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRPLGKGKFGNVYLA
gi|13653970|        PLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRPLGKGKFGNVYLA
gi|4507275|         PLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRPLGKGKFGNVYLA
gi|7446411|         PLPSAPENNPEEELASKQKNEESKKRQWALEDFEIGRPLGKGKFGNVYLA
gi|4507279|         PLPSHLKIILRRNWHQNRK-MKNQKEAVALEDFEIGRPLGKGKFGNVYLA

                    160       170       180       190       200
                    ....|....|....|....|....|....|....|....|....|....|
NOV4                REKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLQHPNIIRLYGYF
gi|12654873|        REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYF
gi|13653970|        REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYF
gi|4507275|         REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYF
gi|7446411|         REKQSKGILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYF
gi|4507279|         REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNILRLYGYF

                    210       220       230       240       250
                    ....|....|....|....|....|....|....|....|....|....|
NOV4                HDATRVYLILEYTPLETVNTELQKLSKFDEQRTATYITELASALSYCHSK
gi|12654873|        HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSYCHSK
gi|13653970|        HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSYCHSK
gi|4507275|         HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSYCHSK
gi|7446411|         HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSYCHSK
gi|4507279|         HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTANLYNRIANALSYCHSF

                    260       270       280       290       300
                    ....|....|....|....|....|....|....|....|....|....|
NOV4                TVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
```

```
gi|12654873|  RVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|13653970|  RVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|4507275|   RVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|7446411|   RVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|4507279|   RVIHRDIKPENLLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM

                      310       320       330       340       350
                      ....|....|....|....|....|....|....|....|....|
NOV4                  IEGRMHDEKVDLWSLGVLCCEFLVGKPPFEANTYQETYKRISRVEFTFPD
gi|12654873|          IEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPD
gi|13653970|          IEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPD
gi|4507275|           IEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPD
gi|7446411|           IEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPD
gi|4507279|           IEGRMHDEKVDLWSLGVLCYEFLVGKPPFEANTYQETYKRISRVEFTFPD

                      360       370       380       390       400
                      ....|....|....|....|....|....|....|....|....|
NOV4                  FVTEGARDLISRLLKHVPSQRPMLREVLEYPWITANSSKPSNCQNKESTS
gi|12654873|          FVTEGARDLISRLLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|13653970|          FVTEGARDLISRLLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|4507275|           FVTEGARDLISRLLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|7446411|           FVTEGARDLISRLLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|4507279|           FVTEGARDLISRLLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS

                      ...
NOV4                  KYS
gi|12654873|          KQS
gi|13653970|          KQS
gi|4507275|           KQS
gi|7446411|           KQS
gi|4507279|           KQS
```

Tables 4E-G lists the domain description from DOMAIN analysis results against NOV4. This indicates that the NOV4 sequence has properties similar to those of other proteins known to contain this domain.

Table 4E Domain Analysis of NOV4

gnl|Smart|smart00220, S_TKc, Serine/Threonine protein kinases, catalytic domain; Phosphotransferases. Serine or threonine-specific kinase subfamily. (SEQ ID NO:98)
CD-Length = 256 residues, 99.6% aligned
Score = 256 bits (653), Expect = 2e-69

```
NOV 3:  134  EIGRPPGKGKFGNVYLAREKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLQHPNI  193
             |+    |||  ||  |||||+|++  ++|++|+ | +|+|     ++ ||++|   | ||||
Sbjct:  2    ELLEVLGKGAFGKVYLARDKKTGKLVAIKVIKKEKLKK-KKRERILREIKILKKLDHPNI  60

NOV 3:  194  IRLYGYFHDATRVYLILEYTPLETVNTELQKLSKFDEQRTATYITELASALSYCHSKTVI  253
             ++||  | |  ++||++||     +   |+|  +  |      |  ++ ||| | ||+ +|
Sbjct:  61   VKLYDVFEDDDKLYLVMEYCEGGDLFDLLKKRGRLSEDEARFYARQILSALEYLHSQGII  120

NOV 3:  254  HRDIKPENLLLGSAGELEIANFGWS--EHAPSSRRTTLCGTLDYLPPEMIEGRMHDEKVD  311
             |||+||||+||  | | +++|+|| +    +  +  ||  || +|+ ||++ |+ + + ||
Sbjct:  121  HRDLKPENILLDSDGHVKLADFGLAKQLDSGGTLLTTFVGTPEYMAPEVLLGKGYGKAVD  180

NOV 3:  312  LWSLGVLCCEFLVGKPPFEA-NTYQETYKRISRVEFTFPDF---VTEGARDLISRLLKHV  367
             +|||||+  | | |||||   +     +|+| +    ||     ++  |+|||  +||
Sbjct:  181  IWSLGVILYELLTGKPPFPGDDQLLALFKKIGKPPPPFPPPEWKISPEAKDLIKKLLVKD  240
```

```
NOV 3:  368  PSQRPMLREVLEYPWI  383
             | +|    | ||+|+
Sbjct:  241  PEKRLTAEEALEHPFF  256
```

Table 4F Domain Analysis of NOV4

gnl|Pfam|pfam00069, pkinase, Protein kinase domain (SEQ ID NO:99)
CD-Length = 256 residues, 100.0% aligned
Score = 221 bits (564), Expect = 5e-59

```
NOV 3:  133  LEIGRPPGKGKFGNVYLAREKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLQHPN  192
             |+|   | | || ||  + | +  |+|+++| |  | +   + +  ||++|   | |||
Sbjct:  1    YELGEKLGSGAFGKVYKGKHKDTGEIVAIKILKKRSLSE--KKKRFLREIQILRRLSHPN  58

NOV 3:  193  IIRLYGYFHDATRVYLILEYTPLETVNTEL-QKLSKFDEQRTATYITELASALSYCHSKT  251
             |+|| | | +   +||++||     +   | +      |+       ++   | | ||+
Sbjct:  59   IVRLLGVFEEDDHLYLVMEYMEGGDLFDYLRRNGLLLSEKEAKKIALQILRGLEYLHSRG  118

NOV 3:  252  VIHRDIKPENLLLGSAGELEIANFGWS---EHAPSSRRTTLCGTLDYLPPEMIEGRMHDE  308
             ++|||+||||+||   | ++||+|| +   | +   + ||  || +|+ ||++||| +
Sbjct:  119  IVHRDLKPENILLDENGTVKIADFGLARKLESSSYEKLTTFVGTPEYMAPEVLEGRGYSS  178

NOV 3:  309  KVDLWSLGVLCCEFLVGKPPFEANTYQETYKRI---SRVEFTFPDFVTEGARDLISRLLK  365
             |||+|||||+  | | || ||    .  |   ||    |+    |  +|  +||| + |
Sbjct:  179  KVDVWSLGVILYELLTGKLPFPGIDPLEELFRIKERPRLRLPLPPNCSEELKDLIKKCLN  238

NOV 3:  366  HVPSQRPMLREVLEYPWI  383
               | +||  +|+| +||
Sbjct:  239  KDPEKRPTAKEILNHPWF  256
```

Table 4G Domain Analysis of NOV4

gnl|Smart|smart00219, TyrKc, Tyrosine kinase, catalytic domain; Phosphotransferases. Tyrosine-specific kinase subfamily (SEQ ID NO:100)
CD-Length = 258 residues, 99.6% aligned
Score = 127 bits (318), Expect = 2e-30

```
NOV 3:  133  LEIGRPPGKGKFGNVYLAREKQSKFILALRVLFKAQLEKAGVEHQ--LRREVEIQSHLQH  190
             | +|+  |+| || ||    |    + + |  |   | |  +      ||  +   | |
Sbjct:  1    LTLGKKLGEGAFGEVYKGTLKGKGGVE-VEVAVKTLKEDASEQQIEEFLREARLMRKLDH  59

NOV 3:  191  PNIIRLYGYFHDATRVYLILEYTPLETVNTELQKLSK--FDEQRTATYITELASALSYCH  248
             |||++| |   +   + +++||     +   |+|           ++  ++|  + |
Sbjct:  60   PNIVKLLGVCTEEEPLMIVMEYMEGGDLLDYLRKNRPKELSLSDLLSFALQIARGMEYLE  119

NOV 3:  249  SKTVIHRDIKPENLLLGSAGELEIANFGWSEHAPSSRRTTLCGTLD----YLPPEMIEGR  304
             ||  +|||+   | |+|    ++||+|| +            +      ++ || ++
Sbjct:  120  SKNFVHRDLAARNCLVGENKTVKIADFGLARDLYDDDYYRKKKSPRLPIRWMAPESLKDG  179

NOV 3:  305  MHDEKVDLWSLGVLCCE-FLVGKPPFEANTYQETYKRISRVEF-TFPDFVTEGARDLISR  362
                | |+|| |||  | | +|+ |+   + +|  + + +      |    +   ||+ +
Sbjct:  180  KFTSKSDVWSFGVLLWEIFTLGESPYPGMSNEEVLEYLKKGYRLPQPPNCPDEIYDLMLQ  239

NOV 3:  363  LLKHVPSQRPMLREVLEY  380
               .      |  ||   |++|
Sbjct:  240  CWAEDPEDRPTFSELVER  257
```

Amplification of chromosome 20q DNA has been reported in a variety of cancers. DNA amplification on 20q13 has also been correlated with poor prognosis among axillary node-negative breast tumor cases. Sen et al. (1997) cloned a partial cDNA encoding STK15 (also known as BTAK and aurora2) from this amplicon and found that it is amplified and overexpressed in 3 human breast cancer cell lines. STK15 encodes a centrosome-associated kinase. Zhou et al. (1998) found that STK15 is involved in the induction of centrosome duplication-distribution abnormalities and aneuploidy in mammalian cells. Centrosomes appear to maintain genomic stability through the establishment of bipolar spindles during cell division, ensuring equal segregation of replicated chromosomes to 2 daughter cells. Deregulated duplication and distribution of centrosomes are implicated in chromosome segregation abnormalities, leading to aneuploidy seen in many cancer cell types. Zhou et al. (1998) found amplification of STK15 in approximately 12% of primary breast tumors, as well as in breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer cell lines. Additionally, high expression of STK15 mRNA was detected in tumor cell lines without evidence of gene amplification. Ectopic expression of STK15 in mouse NIH 3T3 cells led to the appearance of abnormal centrosome number (amplification) and transformation in vitro. Finally, overexpression of STK15 in near-diploid human breast epithelial cells revealed similar centrosome abnormality, as well as induction of aneuploidy. These findings suggested that STK15 is a critical kinase-encoding gene, whose overexpression leads to centrosome amplification, chromosomal instability, and transformation in mammalian cells. Zhou et al. (1998) found that the open reading frame of the full-length STK15 cDNA sequence encodes a 403-amino acid protein with a molecular mass of approximately 46 kD. STK6 (602687), also referred to as AIK, is highly homologous to STK15. The Drosophila 'aurora' and S. cerevisiae Ipl1 STKs are involved in mitotic events such as centrosome separation and chromosome segregation. Using a degenerate primer-based PCR method to screen for novel STKs, Shindo et al. (1998) isolated mouse and human cDNAs encoding STK15, which they termed ARK1 (aurora-related kinase-1). Cell cycle and Northern blot analyses showed that peak expression of STK15 occurs during the G2/M phase and then decreases. By interspecific backcross mapping, Shindo et al. (1998) mapped the mouse Stk15 gene to the distal region of chromosome 2 in a region showing homology of synteny with human 20q

The disclosed NOV4 nucleic acid of the invention encoding a Aurora-related kinase 1-like protein includes the nucleic acid whose sequence is provided in Table 4A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 4A while still encoding a protein that

maintains its Aurora-related kinase 1-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 5 percent of the bases may be so changed.

The disclosed NOV4 protein of the invention includes the Aurora-related kinase 1-like protein whose sequence is provided in Table 4B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 4B while still encoding a protein that maintains its Aurora-related kinase 1-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 9 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the Aurora-related kinase 1-like protein and nucleic acid (NOV4) disclosed herein suggest that NOV4 may have important structural and/or physiological functions characteristic of the citron kinase-like family. Therefore, the NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer, Cardiomyopathy, Atherosclerosis, Hypertension, Congenital heart defects, Aortic stenosis, Atrial septal defect (ASD), Atrioventricular (A-V) canal defect, Ductus arteriosus, Pulmonary

stenosis, Subaortic stenosis, Ventricular septal defect (VSD), valve diseases, Tuberous sclerosis, Scleroderma, Obesity, Transplantation, Diabetes, Von Hippel-Lindau (VHL) syndrome, Pancreatitis, Alzheimer's disease, Stroke, hypercalceimia, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Lesch-Nyhan syndrome, Multiple sclerosis, Ataxia-telangiectasia, Leukodystrophies, Behavioral disorders, Addiction, Anxiety, Pain, and Neuroprotection and/or other pathologies. The NOV4 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV4 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV4 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV4 epitope is from about amino acids 1 to 10. In another embodiment, a NOV4 epitope is from about amino acids 15 to 160. In additional embodiments, NOV4 epitopes are from about amino acids 175 to 210, from about amino acids 220 to 240, from about amino acids 250 to 270, from about amino acids 280 to 320, from about amino acids 340 to 375, and from about amino acids 380 to 400. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV5

A disclosed NOV5 nucleic acid of 1500 nucleotides (designated CuraGen Acc. No. SC44326718_A) encoding a novel 26S protease regulatory subunit 4-like protein is shown in Table 5A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 101-103 and ending with a TAG codon at nucleotides 1427-1429. A putative untranslated region downstream from the termination codon is underlined in Table 5A, and the start and stop codons are in bold letters.

Table 5A. NOV5 Nucleotide Sequence (SEQ ID NO:15)

GTATCCCCAAGAGAAAATACGCATCAAAAATTAGGAACTTAGAAATGATAGTTGAGGTGGAGGAACTTCC
AGCAGTGGCAGCTCAAGTGGCCAAGACAAG**ATG**GGTCAAAGTCAGGGTGATGGTCATGGTCCTAGACGTG
GCAAGAAGGATGAAAAGGACAAGAAAAATAAGTACGAACCTCTTGTACCAACTAGAGTGGCGGAAAAAGA
AGAAAAAACAAAGGGACAAGATGTTGCCAGTAAACTGCCACTGGTGACACTTCACACTCAGTGTCGGTTA
AAATTACTGAAGTTAGAGAGAATTAAAGACTACCTTCTCATGGTGGAAGAATTCATTAGAAATCAGGAAC
AAATAAAACTATTAGAAGAAAAGCAAGAGGAGGGAAGATCAAAAGTGGATGATCTGAGGGGGACCCCAAT

GTCAGTAGGAAACTTGGAAGAGATCATCGATGACAATCATGCCATTGTGTCTACATCTGTGGGCTCAGAA
CACTATGACAGCATTATTTCATTTGTAGAGAAGGATCTGCTGGAACCTGGCTGCTCGATTCTGCTCAGAC
ACAAGGTACATGCGGTGATAGGGGTGCTGATGGATGATACGGGTCCCCTGGTCACAATGATGAAGGTGGA
GAAGGCCCCCCAGGAGACCTATGTCAATACTGGGGGGTTGGACAACCAAATTCAGGAAATTAAGGAATCT
ATGGAGCTTCCTCTCCCCCATCCTGAATATTATGAAGAGATGGGTACAAAGCCTCCTAAAGGGGTCATTC
TCTGTGGTCCACCTGGCACAGGTAAAACCTTGTTAGCCAAAGCAGTAGCAAACCAAACCTCAGCCACTTT
CTTGAGAGTGGTTGGCTCTGAACTTATTCAGAAGTACCTAGGTGATGGGCCCAAACTCGTACGGCAAGTA
TTTCAAGTTGCTGAAGAACATGCACCATCCATCATGTTTACTGATGAAATTGAAGCCATTGGGACAAAAA
GATATGACTCCAATTCTGGTGGTGAGAGAGAAATTCAGCAAACAATGTTGGAATTGGAACTGTTGAACCA
ATTGGGTGGATTTGATTCTAGGGAAGATGTGAAAGTTATCATGGCCACAAAACAAGTAGAAACTTTGGAT
CCAGTACTTATCAGACCAGGCCGCATTGACAAGAAGATCGAGTTCCACCTGCCTGATGAAAAGACTAAGA
AGCACATCTTTCAGATTCACACAAGCAGGATGACACTGGCCAATGATGTAACCCTGGACGACTTGATCAT
GGCTAAAGATGACTTCTCTGGTGCTGACATCAAGGCAATCTGTACAGAAGCTGGTCTGATGGCCTTAAGA
GAACATAGAATGAAAGCAACAAATGAAGACTTCAAAAAATCTATAGAAAGTGTTCTTTATAAGAAACACG
AAGGCATCCCTGAGGGGCTTTATCTCTAGTGAACCACCGCTGCCATCAGGAAGATGGTTGGGAGATTTCC
CAACCCCTGAAAGGGATGAGGTTGGGGGAG

The nucleic acid sequence NOV5, located on chromosome 5 has 1347 of 1447 bases (93%) identical to a gb:GENBANK-ID:HUM26SPSIV|acc:L02426 mRNA from *Homo sapiens* (Human 26S protease (S4) regulatory subunit mRNA, complete cds ($E = 2.4e^{-277}$).

A NOV5 polypeptide (SEQ ID NO:16) encoded by SEQ ID NO:15 is 442 amino acid residues and is presented using the one letter code in Table 5B. Signal P, Psort and/or Hydropathy results predict that NOV5 has no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In other embodiments, NOV5 may also be localized to the microbody (peroxisome) with a certainty of 0.3000, the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 5B. NOV5 protein sequence (SEQ ID NO:16)

MGQSQGDGHGPRRGKKDEKDKKNKYEPLVPTRVAEKEEKTKGQDVASKLPLVTLHTQCRLKLLKLERIKDYLLM
VEEFIRNQEQIKLLEEKQEEGRSKVDDLRGTPMSVGNLEEIIDDNHAIVSTSVGSEHYDSIISFVEKDLLEPGC
SILLRHKVHAVIGVLMDDTGPLVTMMKVEKAPQETYVNTGGLDNQIQEIKESMELPLPHPEYYEEMGTKPPKGV
ILCGPPGTGKTLLAKAVANQTSATFLRVVGSELIQKYLGDGPKLVRQVFQVAEEHAPSIMFTDEIEAIGTKRYD
SNSGGEREIQQTMLELELLNQLGGFDSREDVKVIMATKQVETLDPVLIRPGRIDKKIEFHLPDEKTKKHIFQIH
TSRMTLANDVTLDDLIMAKDDFSGADIKAICTEAGLMALREHRMKATNEDFKKSIESVLYKKHEGIPEGLYL

The full amino acid sequence of the protein of the invention was found to have 383 of 442 amino acid residues (86%) identical to, and 405 of 442 amino acid residues (91%) similar to, the 440 amino acid residue ptnr:SWISSPROT-ACC:P49014 protein from *Mus musculus* (Mouse), and *Rattus norvegicus* (Rat) (26S Protease Regulatory Subunit 4 (P26S4) ($E = 1.7e^{-200}$).

NOV5 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 5C.

Table 5C. BLAST results for NOV5

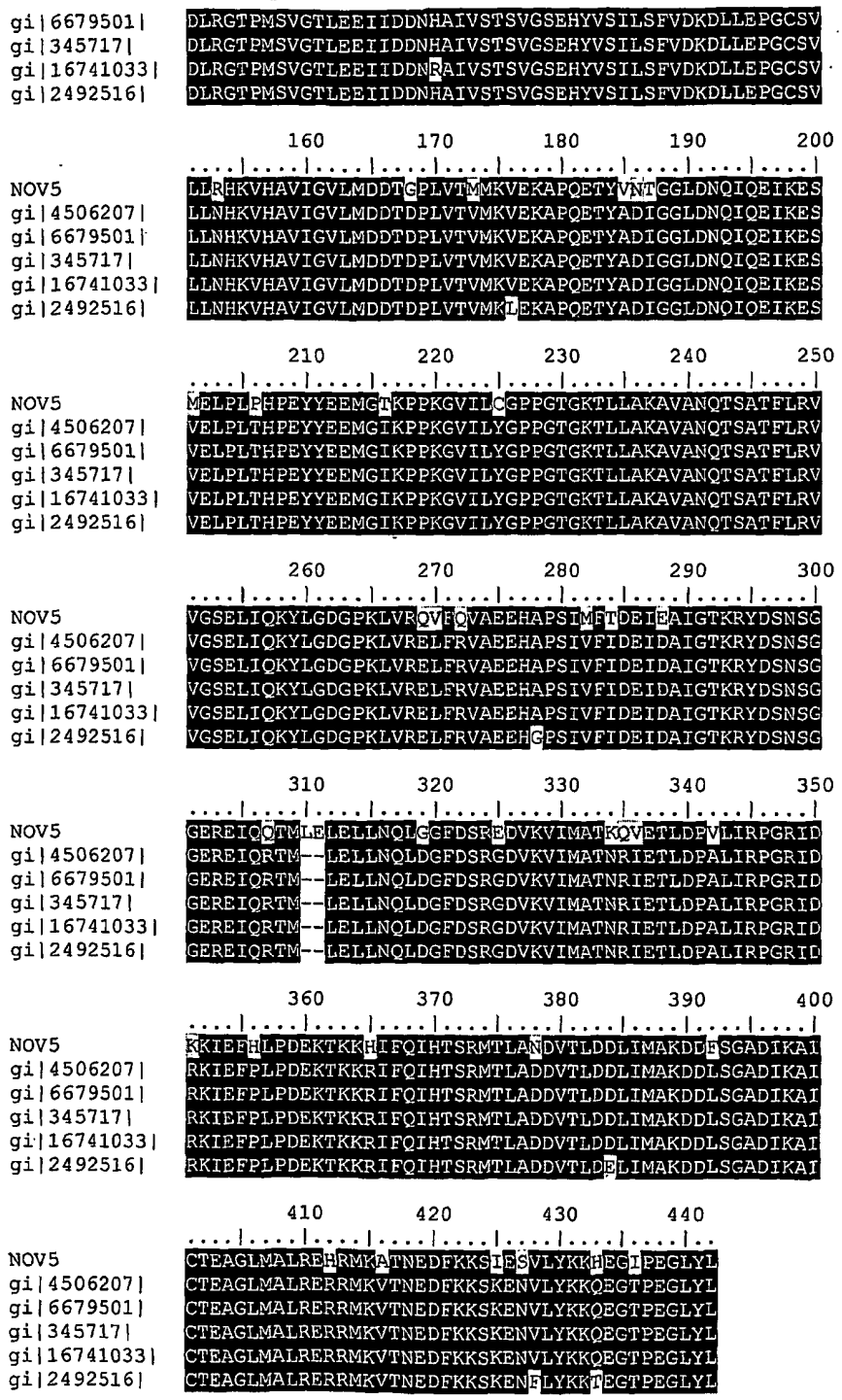
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|4506207|ref|NP_002793.1| (NM_002802)	proteasome (prosome, macropain) 26S subunit, ATPase, 1; Proteasome 26S subunit, ATPase, 1 [Homo sapiens]	440	382/442 (86%)	405/442 (91%)	0.0
gi|6679501|ref|NP_032973.1| (NM_008947)	protease (prosome, macropain) 26S subunit, ATPase 1 [Mus musculus]	440	383/442 (86%)	405/442 (90%)	0.0
gi|345717|pir||A44468	26S proteasome regulatory chain 4 [validated] - human	440	381/442 (86%)	404/442 (91%)	0.0
gi|16741033|gb|AAH16368.1|AAH16368 (BC016368)	protease (prosome, macropain) 26S subunit, ATPase 1 [Homo sapiens]	440	382/442 (86%)	404/442 (90%)	0.0
gi|2492516|sp|Q90732|PRS4_CHICK	26S PROTEASE REGULATORY SUBUNIT 4 (P26S4)	440	378/442 (85%)	402/442 (90%)	0.0

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 5D.

Table 5D ClustalW Analysis of NOV5

1) NOV5 (SEQ ID NO:16)
2) gi|4506207|ref|NP_002793.1| (NM_002802) proteasome (prosome, macropain) 26S subunit, ATPase, 1; Proteasome 26S subunit, ATPase, 1 [Homo sapiens] (SEQ ID NO:52)
3) gi|6679501|ref|NP_032973.1| (NM_008947) protease (prosome, macropain) 26S subunit, ATPase 1 [Mus musculus] (SEQ ID NO:53)
4) gi|345717|pir||A44468 26S proteasome regulatory chain 4 [validated] - human (SEQ ID NO:54)
5) gi|16741033|gb|AAH16368.1|AAH16368 (BC016368) protease (prosome, macropain) 26S subunit, ATPase 1 [Homo sapiens] (SEQ ID NO:55)
6) gi|2492516|sp|Q90732|PRS4_CHICK 26S PROTEASE REGULATORY SUBUNIT 4 (P26S4) (SEQ ID NO:56)

```
                        10        20        30        40        50
                ....|....|....|....|....|....|....|....|....|....|
NOV5            MGQSQGDGHGPRRGKKDEKDKKNKYEPLVPTRVAEKEEKTKGQDVASKLP
gi|4506207|     MGQSQSGGHGPGGGKKDDEDKKKKYEPPVPTRVGKKKKKTKGPDAASKLP
gi|6679501|     MGQSQSGGHGPGGGKKDDKDKKKKYEPPVPTRVGKKKKKTKGPDAASKLP
gi|345717|      MGQSQSGGHGPGGGKKDDEDKKKKYEPPVPTRVGKKKKKRKGPDAASKLP
gi|16741033|    MGQSQSGGHGPGGGKKDDKDKKKKYEPPVPTRVGKKKKKTKGPDAASKLP
gi|2492516|     MGQSQSGGHGPGGGKKDDKDKKKKYEPPVPTRVGKKKKKTKGPDAASKPP

                        60        70        80        90       100
                ....|....|....|....|....|....|....|....|....|....|
NOV5            LVTLHTQCRLKLLKLERIKDYLLMVEEFIRNQEQIKLLEEKQEEGRSKVD
gi|4506207|     LVTPHTQCRLKLLKLERIKDYLLMEEEFIRNQEQMKPLEEKQEEERSKVD
gi|6679501|     LVTPHTQCRLKLLKLERIKDYLLMEEEFIRNQEQMKPLEEKQEEERSKVD
gi|345717|      LVTPHTQCRLKLLKLERIKDYLLMEEEFIRNQEQMKPLEEKQEEERSKVD
gi|16741033|    LVTPHTQCRLKLLKLERIKDYLLMEEEFIRNQEQMKPLEEKQEEERSKVD
gi|2492516|     LVTPHTQCRLKLLKLERIKDYLLMEEEFIRNQEQMKPLEEKQEEERSKVD

                       110       120       130       140       150
                ....|....|....|....|....|....|....|....|....|....|
NOV5            DLRGTPMSVGNLEEIIDDNHAIVSTSVGSEHYDSIISFVEKDLLEPGCSI
gi|4506207|     DLRGTPMSVGTLEEIIDDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSV
```



Tables 5E-F list the domain description from DOMAIN analysis results against NOV5. This indicates that the NOV5 sequence has properties similar to those of other proteins known to contain this domain.

Table 5E. Domain Analysis of NOV5

gnl|Pfam|pfam00004, AAA, ATPase family associated with various cellular activities (AAA). AAA family proteins often perform chaperone-like functions that assist in the assembly, operation, or disassembly of protein complexes (SEQ ID NO:101)
CD-Length = 186 residues, 100.0% aligned
Score = 190 bits (483), Expect = 1e-49

```
NOV 4:  221  GVILCGPPGTGKTLLAKAVANQTSATFLRVVGSELIQKYLGDGPKLVRQVFQVAEEHAPS  280
             |++| ||||||||||||||| +    |+ + ||||+ ||+|+  |||| +| +| + ||
Sbjct:  1    GILLYGPPGTGKTLLAKAVAKELGVPFIEISGSELLSKYVGESEKLVRALFSLARKSAPC  60

NOV 4:  281  IMFTDEIEAIGTKRYDSNSGGEREIQQTMLELELLNQLGGFDSREDVKVIMATKQVETLD  340
             |+| |||+|+  || |  +|         +  +|| ++ ||+   +| || || + + ||
Sbjct:  61   IIFIDEIDALAPKRGDVGTGDVSS----RVVNQLLTEMDGFEKLSNVIVIGATNRPDLLD  116

NOV 4:  341  PVLIRPGRIDKKIEFHLPDEKTKKHIFQIHTSRMTLANDVTLDDLIMAKDDFSGADIKAI  400
             | |+|||| |++||  ||||+ +  | +||  +  |  || ||++      |||||+ |+
Sbjct:  117  PALLRPGRFDRRIEVPLPDEEERLEILKIHLKKKPLEKDVDLDEIARRTPGFSGADLAAL  176

NOV 4:  401  CTEAGLMALR  410
             | || | |+|
Sbjct:  177  CREAALRAIR  186
```

Table 5F. Domain Analysis of NOV5

gnl|Smart|smart00382, AAA, ATPases associated with a variety of cellular activities; AAA. This profile/alignment only detects a fraction of this vast family. The poorly conserved N-terminal helix is missing from the alignment. (SEQ ID NO:102)
CD-Length = 151 residues, 100.0% aligned
Score = 61.6 bits (148), Expect = 9e-11

```
NOV 4:  218  PPKGVILCGPPGTGKTLLAKAVANQTSATFLRVV----------GSELIQK  258
             | + |++ ||||+||| ||+|+| +       |+                |
Sbjct:  1    PGEVVLIVGPPGSGKTTLARALARELGPDGGGVIYIDGEDLREEALLQLLRLLVLVGEDK  60

NOV 4:  259  YLGDGPKLVRQVFQVAEEHAPSIMFTDEIEAIGTKRYDSNSGGEREIQQTMLELELLNQL  318
               | + +|    +| +  | ++  ||| ++     +           +|  |||  |
Sbjct:  61   LSGSGGQRIRLALALARKLKPDVLILDEITSLLDAEQE---------ALLLLEELLRLL  111

NOV 4:  319  GGFDSREDVKVIMATKQVETLDPVLIRPGRIDKKIEFHLPD  359
                  |+| ||  |     | | |+|  | |++|
Sbjct:  112  LLLLKEENVTVIATTNDETDLIPALLRR-RFDRRIVLLRIL  151
```

Ubiquitinated proteins are degraded by a 26S ATP-dependent protease. The protease is composed of a 20S catalytic proteasome and 2 PA700 regulatory modules. The PA700 complex is composed of multiple subunits, including at least 6 related ATPases and approximately 15 non-ATPase polypeptides. Tanahashi et al. (1998) stated that each of the 6 ATPases, namely PSMC1, PSMC2 (154365), PSMC3 (186852), PSMC4 (602707), PSMC5 (601681), and PSMC6 (602708), contains an AAA (ATPases associated with diverse cellular activities) domain (see PSMC5). Dubiel et al. (1992) cloned cDNAs encoding subunit 4 (S4) of the 26S protease by screening a HeLa cell cDNA library with probes that were produced

using the protein sequence. The 440-amino acid protein has a molecular mass of 51 kD by SDS-PAGE. By fluorescence in situ hybridization, Tanahashi et al. (1998) mapped the human PSMC1 gene to 19p13.3. Hoyle and Fisher (1996) found that the human and mouse PSMC1 proteins have 99% amino acid identity. They reported that the mouse Psmc1 gene contains at least 11 exons. By analysis of an interspecific backcross, Hoyle and Fisher (1996) mapped the mouse Psmc1 gene to chromosome 12. Nomenclature note: The PSMC1 gene product, which Dubiel et al. (1992) called subunit 4 (S4), is distinct from the PSMC4 (602707) gene product.

The disclosed NOV5 nucleic acid of the invention encoding a 26S protease regulatory subunit 4 -like protein includes the nucleic acid whose sequence is provided in Table 5A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 5A while still encoding a protein that maintains its 26S protease regulatory subunit 4 -like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 7 percent of the bases may be so changed.

The disclosed NOV5 protein of the invention includes the 26S protease regulatory subunit 4 -like protein whose sequence is provided in Table 5B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 5B while still encoding a protein that maintains its 26S protease regulatory subunit 4 -like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 14 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the 26S protease regulatory subunit 4-like protein and nucleic acid (NOV5) disclosed herein suggest that this NOV5 protein may have important structural and/or physiological functions characteristic of the 26S protease regulatory subunit 4 family. Therefore, the NOV5 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic

applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV5 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from cataract and Aphakia, Alzheimer's disease, neurodegenerative disorders, inflammation and modulation of the immune response, viral pathogenesis, aging-related disorders, neurologic disorders, cancer and/or other pathologies. The NOV5 nucleic acids, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV5 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example, the disclosed NOV5 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV5 epitope is from about amino acids 5 to 50. In another embodiment, a NOV5 epitope is from about amino acids 75 to 125. In additional embodiments, NOV5 epitopes are from about amino acids 175 to 225, from about amino acids 280 to 320, from about amino acids 330 to 380, and from about amino acids 390 to 440. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV6

A disclosed NOV6 nucleic acid of 1020 nucleotides (also referred to as GMAC073364_A_da1) encoding a novel MITSUGUMIN29-like protein is shown in Table 6A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 2-4 and ending with a TAA codon at nucleotides 818-820. Putative untranslated

regions upstream from the initiation codon and downstream from the termination codon are underlined in Table 6A, and the start and stop codons are in bold letters.

Table 6A. NOV6 Nucleotide Sequence (SEQ ID NO:17)

CATGTCCTCGACCGAGAGCGCCGGCCGCACGGCGGACAAGTCGCCGCGCCAGCAGGTGGACC
GCCTACTCGTGGGGCTGCGCTGGCGGCGGCTGGAGGAGCCGCTGGGCTTCATCAAAGTTCTC
CAGTGGCTCTTTGCTATTTTCGCCTTCGGGTCCTGTGGCTCCTACAGCGGGGAGACAGGAGC
AATGGTTCGCTGCAACAACGAAGCCAAGGACGTGAGCTCCATCATCGTTGCATTTGGCTATC
CCTTCAGGTTGCACCGGATCCAATATGAGATGCCCCTCTGCGATGAAGAGTCCAGCTCCAAG
ACCATGCACCTCATGGGGGACTTCTCTGCACCCGCCGAGTTCTTCGTGACCCTTGGCATCTT
TTCCTTCTTCTATACCATGGCTGCCCTAGTTATCTACCTGCGCTTCCACAACCTCTACACAG
AGAACAAACGCTTCCCGCTGGTGGACTTCTGTGTGACTGTCTCCTTCACCTTCTTCTGGCTG
GTAGCTGCAGCTGCCTGGGGCAAGGGCCTGACCGATGTCAAGGGGGCCACACGACCATCCAG
CTTGACAGCAGCCATGTCAGTGTGCCATGGAGAGGAAGCAGTGTGCAGTGCCGGGGCCACGC
CCTCTATGGGCCTGGCCAACATCTCCGTGCTCTTTGGCTTTATCAACTTCTTCCTGTGGGCC
GGGAACTGTTGGTTTGTGTTCAAGGAGACCCCGTGGCATGGACAGGGCCAGGGCCAGGACCA
GGACCAGGACCAGGACCAGGGCCAGGGTCCCAGCCAGGAGAGTGCAGCTGAGCAGGGAGCAG
TGGAGAAGCAGTAAGCAGCCCCCCACCT

The NOV6 nucleic acid was identified on chromosome 3 and has 727 of 805 bases (90%) identical to a gb:GENBANK-ID:AB004816|acc:AB004816.1 mRNA from *Oryctolagus cuniculus* (*Oryctolagus cuniculus* mRNA for mitsugumin29, complete cds ($E = 2.5e^{-142}$).

A disclosed NOV6 polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 272 amino acid residues and is presented using the one-letter code in Table 6B. Signal P, Psort and/or Hydropathy results predict that NOV6 has a signal peptide and is likely to be localized on the plasma membrane with a certainty of 0.6000. In other embodiments, NOV6 may also be localized to the Golgi body with acertainty of 0.4000, the endoplasmic reticulum (membrane) with a certainty of 0.3000, or the nucleus with a certainty of 0.1000. The most likely celavage site for NOV6 is between positions 57 and 58, SYS-GE.

Table 6B. Encoded NOV6 protein sequence (SEQ ID NO:18)

MSSTESAGRTADKSPRQQVDRLLVGLRWRRLEEPLGFIKVLQWLFAIFAFGSCGSYSGETGAMVRCNNEAKD
VSSIIVAFGYPFRLHRIQYEMPLCDEESSSKTMHLMGDFSAPAEFFVTLGIFSFFYTMAALVIYLRFHNLYT
ENKRFPLVDFCVTVSFTFFWLVAAAAWGKGLTDVKGATRPSSLTAAMSVCHGEEAVCSAGATPSMGLANISV
LFGFINFFLWAGNCWFVFKETPWHGQGQGQDQDQDQDQGQGPSQESAAEQGAVEKQ

The disclosed NOV6 amino acid sequence has 727 of 805 amino acid residues (90%) identical to, and 727 of 805 amino acid residues (90%) similar to, the 3489 amino acid residue gb:GENBANK-ID:AB004816|acc:AB004816.1 protein from *Oryctolagus cuniculus* (*Oryctolagus cuniculus* mRNA for mitsugumin29, complete cds) ($E = 2.5e^{-142}$).

Based on the semi quantitative PCR, NOV6 is specially expressed in: Skeletal muscle, Heart, Kidney, Adrenal gland and one of the Lung cancer cell lines (Lung cancer NCI-H522) at a measurably higher level than the following tissues: Endothelial cells, Pancreas, Thyroid,

Salivary gland, Pituitary gland, Brain (fetal), Brain (whole), Brain (amygdala), Brain (cerebellum), Brain (hippocampus), Brain (thalamus), Cerebral Cortex, Spinal cord, Bone marrow, Thymus, Spleen, Lymph node, Colorectal, Stomach, Small intestine, Bladder, Trachea, Kidney (fetal), Liver, Liver (fetal), Lung, Lung (fetal), Mammary gland, Ovary, Uterus, Placenta, Prostate, Testis, Melanoma, Adipose and cancer cell lines including Breast cancer, CNS cancer, Colon cancer, Gastric cancer, Lung cancer (except Lung cancer NCI-H522), Ovarian cancer, Pancreatic cancer, and Renal cancer.

In addition, NOV6 is predicted to be expressed in skeletal muscle because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AB004816|acc:AB004816.1) a closely related mitsugumin29 homolog in *Oryctolagus cuniculus*.

NOV6 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 6C.

Table 6C. BLAST results for NOV6

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|3077703|dbj|BAA25784.1| (AB004816)	mitsugumin29 [Oryctolagus cuniculus]	264	252/272 (92%)	256/272 (93%)	e-136
gi|6678874|ref|NP_032622.1| (NM_008596)	mitsugumin 29 [Mus musculus]	264	246/272 (90%)	258/272 (94%)	e-133
gi|12836843|dbj|BAB23831.1| (AK005132)	putative [Mus musculus]	285	118/251 (47%)	158/251 (62%)	7e-59
gi|1351168|sp|P20488|SYPH_BOVIN	SYNAPTOPHYSIN (MAJOR SYNAPTIC VESICLE PROTEIN P38)	307	109/221 (49%)	145/221 (65%)	3e-58
gi|2134413|pir||I50720	synaptophysin IIa - chicken	268	109/217 (50%)	142/217 (65%)	4e-57

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 6D.

Table 6D Clustal W Sequence Alignment

1) NOV6 (SEQ ID NO:18)
2) gi|3077703|dbj|BAA25784.1| (AB004816) mitsugumin29 [Oryctolagus cuniculus] (SEQ ID NO:57)
3) gi|6678874|ref|NP_032622.1| (NM_008596) mitsugumin 29 [Mus musculus] (SEQ ID NO:58)
4) gi|12836843|dbj|BAB23831.1| (AK005132) putative [Mus musculus] (SEQ ID NO:59)
5) gi|1351168|sp|P20488|SYPH_BOVIN SYNAPTOPHYSIN (MAJOR SYNAPTIC VESICLE PROTEIN P38) (SEQ ID NO:60)
6) gi|2134413|pir||I50720 synaptophysin IIa - chicken (SEQ ID NO:61)

```
                        10        20        30        40        50
                 ....|....|....|....|....|....|....|....|....|....|
NOV6             MSSTESAGRTADKSPRQQVDRLLVGLRWRRLEEPLGFIKVLQWLFAIFAF
gi|3077703|      MSSTESPSRAADKSPRQQVDRLLEGLRWRRLEEPLGFIKVLQWLFAIFAF
gi|6678874|      MSSTESPGRTSDKSPRQQVDRLLLGLRWQRLEEPLGFIKVLQWLFAIFAF
```

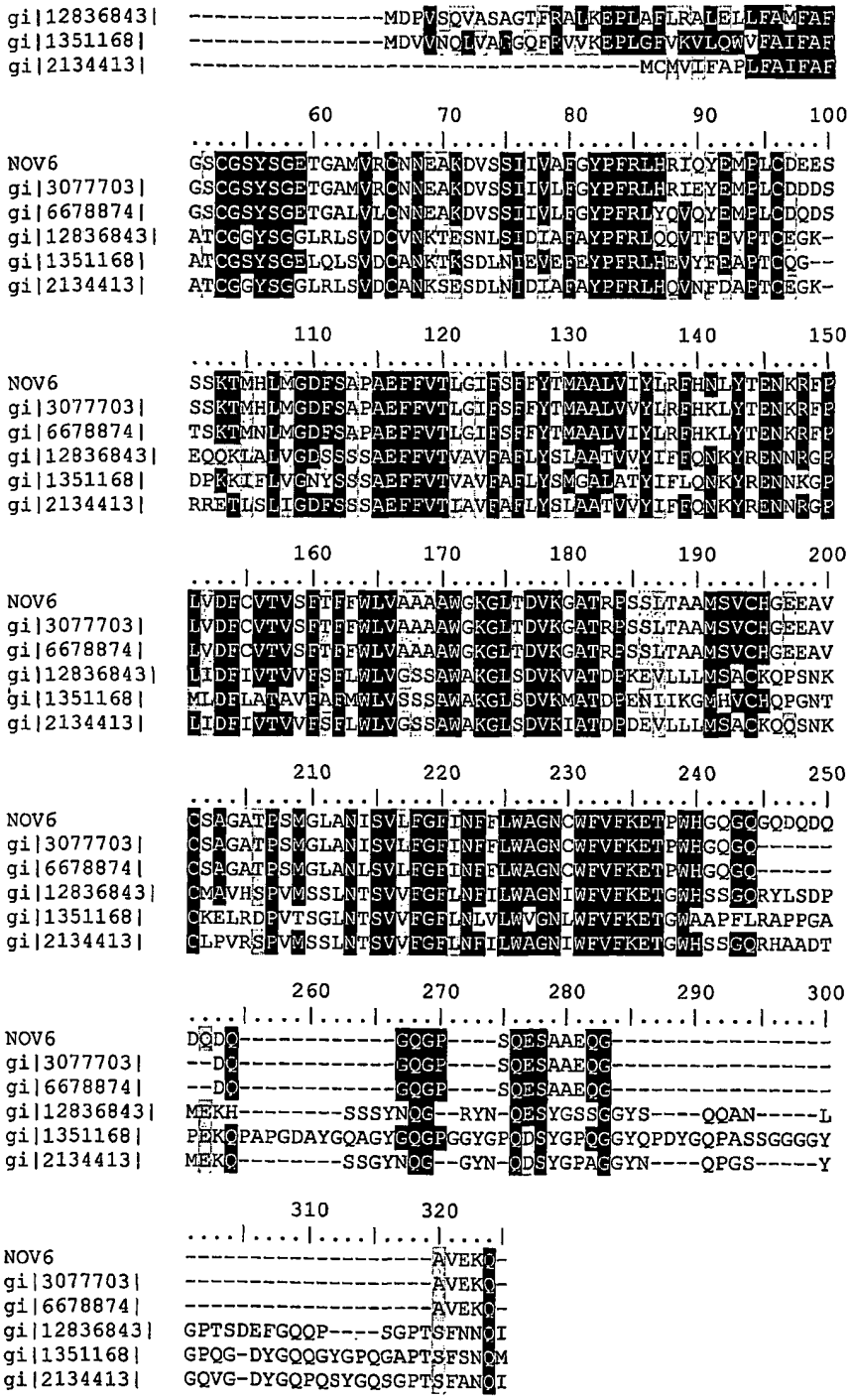


Table 6E lists the domain description from DOMAIN analysis results against NOV6. This indicates that the NOV6 sequence has properties similar to those of other proteins known to contain this domain.

Table 6E. Domain Analysis of NOV6

gnl|Pfam|pfam01284, Synaptophysin, Synaptophysin / synaptoporin. (SEQ ID NO:103)
CD-Length = 298 residues, 70.8% aligned
Score = 244 bits (622), Expect = 6e-66

```
NOV 5:  29   RRLEEPLGFIKVLQWLFAIFAFGSCGSYSGETGAMVRCNNEAKDVSSIIVAFGYPFRLHR  88
Sbjct:  3    MVIFAPLGFVKVLQWVFAIFAFATCGGYSGELQLSVDCANKTESDLNIDIAFAYPFRLHE  62

NOV 5:  89   IQYEMPLCDEESSSKTMHLMGDFSAPAEFFVTLGIFSFFYTMAALVIYLRFHNLYTENKR  148
Sbjct:  63   VTFEAPTC-EGDEKKNIALVGDSSSSAEFFVTVAVFAFLYSLAALATYIFFQNKYRENNK  121

NOV 5:  149  FPLVDFCVTVSFTFFWLVAAAAWGKGLTDVKGATRPSSLTAAMSVCHGEEAVCSAGATPS  208
Sbjct:  122  GPLIDFIATAVFAFLWLVGSSAWAKGLSDVKMATDPEEIIKGMHACHQPGNKCKELHDPV  181

NOV 5:  209  MGLANISVLFGFINFFLWAGNCWFVFKETPWH  240
Sbjct:  182  MSGLNTSVVFGFLNFILWAGNIWFVFKETGWA  213
```

In skeletal muscle, excitation-contraction (E-C) coupling requires the conversion of the depolarization signal of the invaginated surface membrane, namely the transverse (T-) tubule, to Ca2+ release from the sarcoplasmic reticulum (SR) (Takeshima H et al., Biochem J 1998 Apr 1;331 (Pt 1):317-22 / PMID: 9512495, UI: 98180964). Signal transduction occurs at the junctional complex between the T-tubule and SR, designated as the triad junction, which contains two components essential for E-C coupling, namely the dihydropyridine receptor as the T-tubular voltage sensor and the ryanodine receptor as the SR Ca2+-release channel. However, functional expression of the two receptors seemed to constitute neither the signal-transduction system nor the junction between the surface and intracellular membranes in cultured cells, suggesting that some as-yet-unidentified molecules participate in both the machinery. In addition, the molecular basis of the formation of the triad junction is totally unknown. It is therefore important to examine the components localized to the triad junction. Takeshima et al. report the identification using monoclonal antibody and primary structure by cDNA cloning of mitsugumin29, a novel transmembrane protein from the triad junction in skeletal muscle. This protein is homologous in amino acid sequence and shares characteristic structural features with the members of the synaptophysin family. The subcellular distribution and protein structure suggest that mitsugumin29 is involved in communication between the T-tubular and junctional SR membranes.

Physiological roles of the members of the synaptophysin family, carrying four transmembrane segments and being basically distributed on intracellular membranes including synaptic vesicles, have not been established yet (Nishi M et al., J Cell Biol 1999 Dec

27;147(7):1473-80 / PMID: 10613905, UI: 20082885). Recently, mitsugumin29 (MG29) was identified as a novel member of the synaptophysin family from skeletal muscle. MG29 is expressed in the junctional membrane complex between the cell surface transverse (T) tubule and the sarcoplasmic reticulum (SR), called the triad junction, where the depolarization signal is converted to Ca(2+) release from the SR. In this study, Nishi et al. examined biological functions of MG29 by generating knockout mice. The MG29-deficient mice exhibited normal health and reproduction but were slightly reduced in body weight. Ultrastructural abnormalities of the membranes around the triad junction were detected in skeletal muscle from the mutant mice, i.e., swollen T tubules, irregular SR structures, and partial misformation of triad junctions. In the mutant muscle, apparently normal tetanus tension was observed, whereas twitch tension was significantly reduced. Moreover, the mutant muscle showed faster decrease of twitch tension under Ca(2+)-free conditions. The morphological and functional abnormalities of the mutant muscle seem to be related to each other and indicate that MG29 is essential for both refinement of the membrane structures and effective excitation-contraction coupling in the skeletal muscle triad junction. These results further imply a role of MG29 as a synaptophysin family member in the accurate formation of junctional complexes between the cell surface and intracellular membranes.

The temporal appearance and subcellular distribution of mitsugumin29 (MG29), a 29-kDa transmembrane protein isolated from the triad junction in skeletal muscle, were examined by immunohistochemistry during the development of rabbit skeletal muscle (Komazaki S et al., Dev Dyn 1999 Jun;215(2):87-95 / PMID: 10373013, UI: 99300228). MG29 appeared in the sarcoplasmic reticulum (SR) in muscle cells at fetal day 15 before the onset of transverse tubule (T tubule) formation. In muscle cells at fetal day 27, in which T tubule and triad formation is ongoing, both SR and triad were labeled for MG29. In muscle cells at newborn 1 day, the labeling of the SR had become weak and the triads were well developed and clearly labeled for MG29. Specific and clear labeling for MG29 was restricted to the triads in adult skeletal muscle cells. When MG29 was expressed in amphibian embryonic cells by injection of the cRNA, a large quantity of tubular smooth-surfaced endoplasmic reticulum (sER) was formed in the cytoplasm. The tubular sER was 20-40 nm in diameter and appeared straight or reticular in shape. The tubular sER was formed by the fusion of coated vesicles [budded off from the rough-surfaced endoplasmic reticulum (rER)] and vacuoles of rER origin. The present results suggest that MG29 may play important roles both in the formation of the SR and the construction of the triads during the early development of skeletal muscle cells.

Recently mitsugumin29 unique to the triad junction in skeletal muscle was identified as a novel member of the synaptophysin family; the members of this family have four transmembrane segments and are distributed on intracellular vesicles. In this study, Shimuta et al. FEBS Lett 1998 Jul 17;431(2):263-7 / PMID: 9708916, UI: 98372647, isolated and analyzed mouse mitsugumin29 cDNA and genomic DNA containing the gene. The mitsugumin29 gene mapped to the mouse chromosome 3 F3-H2 is closely related to the synaptophysin gene in exon-intron organization, which indicates their intimate relationship in molecular evolution. RNA blot hybridization and immunoblot analysis revealed that mitsugumin29 is expressed abundantly in skeletal muscle and at lower levels in the kidney. Immunofluorescence microscopy demonstrated that mitsugumin29 exists specifically in cytoplasmic regions of the proximal and distal tubule cells in the kidney. The results obtained may suggest that mitsugumin29 is involved in the formation of specialized endoplasmic reticulum systems in skeletal muscle and renal tubule cells.

The disclosed NOV6 nucleic acid of the invention encoding a MITSUGUMIN29 -like protein includes the nucleic acid whose sequence is provided in Table 6A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 6A while still encoding a protein that maintains its MITSUGUMIN29 -like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 10 percent of the bases may be so changed.

The disclosed NOV6 protein of the invention includes the MITSUGUMIN29 -like protein whose sequence is provided in Table 6B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 6B while still encoding a protein that maintains its MITSUGUMIN29-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 10 percent of the residues may be so changed.

The NOV6 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in eye/lens disorders including but not limited to muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalceimia, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy , congenital adrenal hyperplasia, and other diseases, disorders and conditions of the like. Also since the invention is highly expressed in one of the lung cancer cell lines (Lung cancer NCI-H522), it may be useful in diagnosis and treatment of this cancer. The NOV6 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV6 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV6 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV6 epitope is from about amino acids 10 to 40. In other embodiments, NOV6 epitope is from about amino acids 60 to 70, from about amino acids 90 to 130, from about amino acids 145 to 155, from about amino acid 170 to 180, and from about amino acids 220 to 270. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV7

A disclosed NOV7 nucleic acid of 1020 nucleotides (also referred to as 106973211_EXT) encoding a novel Wnt-15-like protein is shown in Table 7A. An open reading frame was identified beginning with an CTG initiation codon at nucleotides 2-4 and ending with a TAG codon at nucleotides 995-997. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 7A, and the start and stop codons are in bold letters. Since the starting codon is not a

traditional initiation codon, NOV7 could represent a partial reading frame, and could further extend in the 5' direction.

Table 7A. NOV7 Nucleotide Sequence (SEQ ID NO:19)

```
CCTGACCGGGCGGGAAGTCCTGACGCCCTTCCCAGGATTGGGCACTGCGGCAGCCCCGGCACAGGGCGGG
GCCCACCTGAAGCAGTGTGACCTGCTGAAGCTGTCCCGGCGGCAGAAGCAGCTCTGCCGGAGGGAGCCCG
GCCTGGCTGAGACCCTGAGGGATGCTGCGCACCTCGGCCTGCTTGAGTGCCAGTTTCAGTTCCGGCATGA
GCGCTGGAACTGTAGCCTGGAGGGCAGGATGGGCCTGCTCAAGAGAGGCTTCAAAGAGACAGCTTTCCTG
TACGCGGTGTCCTCTGCCGCCCTCACCCACACCCTGGCCCGGGCCTGCAGCGCTGGGCGCATGGAGCGCT
GCACCTGTGATGACTCTCCGGGGCTGGAGAGCCGGCAGGCCTGGCAGTGGGGCGTGTGCGGTGACAACCT
CAAGTACAGCACCAAGTTTCTGAGCAACTTCCTGGGGTCCAAGAGAGGAAACAAGGACCTGCGGGCACGG
GCAGACGCCCACAATACCCACGTGGGCATCAAGGCTGTGAAGAGTGGCCTCAGGACCACGTGTAAGTGCC
ATGGCGTATCAGGCTCCTGTGCCGTGCGCACCTGCTGGAAGCAGCTCTCCCCGTTCCGTGAGACGGGCCA
GGTGCTGAAACTGCGCTATGACTCGGCTGTCAAGGTGTCCAGTGCCACCAATGAGGCCTTGGGCCGCCTA
GAGCTGTGGGCCCCTGCCAGGCAGGGCAGCCTCACCAAAGGCCTGGCCCCAAGGTCTGGGGACCTGGTGT
ACATGGAGGACTCACCCAGCTTCTGCCGGCCCAGCAAGTACTCACCTGGCACAGCAGGTAGGGTGTGCTC
CCGGGAGGCCAGCTGCAGCAGCCTGTGCTGCGGGCGGGGCTATGACACCCAGAGCCGCCTGGTGGCCTTC
TCCTGCCACTGCCAGGTGCAGTGGTGCTGCTACGTGGAGTGCCAGCAATGTGTGCAGGAGGAGCTTGTGT
ACACCTGCAAGCACTAGGCCTACTGCCCAGCAAGCCAGTC
```

The disclosed NOV7 nucleic acid sequence , located on chromosome 17, has 688 of 1009 bases (68%) identical to a gb:GENBANK-ID:AF031168|acc:AF031168.1 mRNA from *Gallus gallus* (*Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds) ($E = 3.0e^{-76}$).

A disclosed NOV7 polypeptide (SEQ ID NO:20) encoded by SEQ ID NO:19 is 331 amino acid residues and is presented using the one-letter amino acid code in Table 7B. Signal P, Psort and/or Hydropathy results predict that NOV7 contains no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In other embodiments, NOV7 is also likely to be localized to the microbody (peroxisome) with a certainty of 0.3000, the mtochondrial matrix space with a certainty of 0.1000, or to the lysosome (lumen) with a certainty of 0.1000.

Table 7B. Encoded NOV7 protein sequence (SEQ ID NO:20).

```
LTGREVLTPFPGLGTAAAPAQGGAHLKQCDLLKLSRRQKQLCRREPGLAETLRDAAHLGLLECQFQFRHERWNCS
LEGRMGLLKRGFKETAFLYAVSSAALTHTLARACSAGRMERCTCDDSPGLESRQAWQWGVCGDNLKYSTKFLSNF
LGSKRGNKDLRARADAHNTHVGIKAVKSGLRTTCKCHGVSGSCAVRTCWKQLSPFRETGQVLKLRYDSAVKVSSA
TNEALGRLELWAPARQGSLTKGLAPRSGDLVYMEDSPSFCRPSKYSPGTAGRVCSREASCSSLCCGRGYDTQSRL
VAFSCHCQVQWCCYVECQQCVQEELVYTCKH
```

The disclosed NOV7 amino acid sequence has 205 of 330 amino acid residues (62%) identical to, and 252 of 330 amino acid residues (76%) similar to, the 354 amino acid residue ptnr:SWISSPROT-ACC:O42280 protein from *Gallus gallus* (Chicken) (WNT-14 Protein Precursor) ($E = 1.3e^{-114}$).

The tissue expression of NOV7 is predicted to be expressed in brain because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF031168|acc:AF031168.1) a closely related *Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds homolog.

NOV7 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 7C.

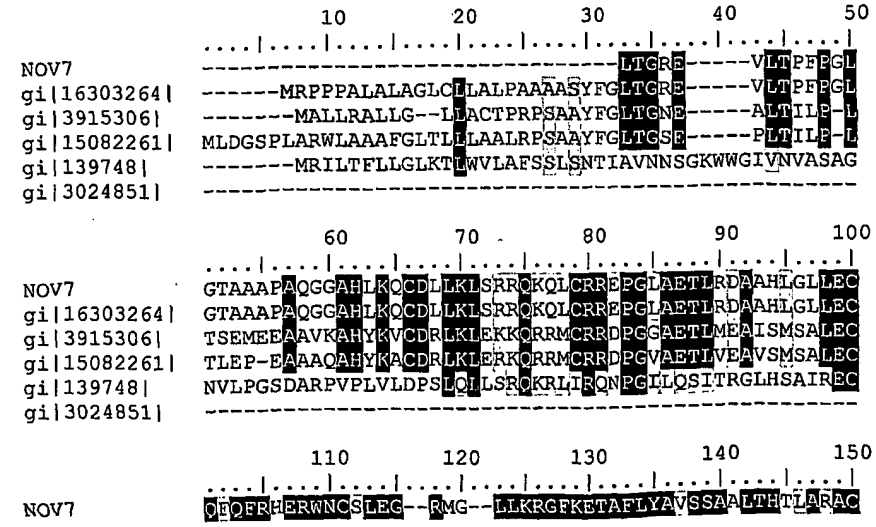
Table 7C. BLAST results for NOV7

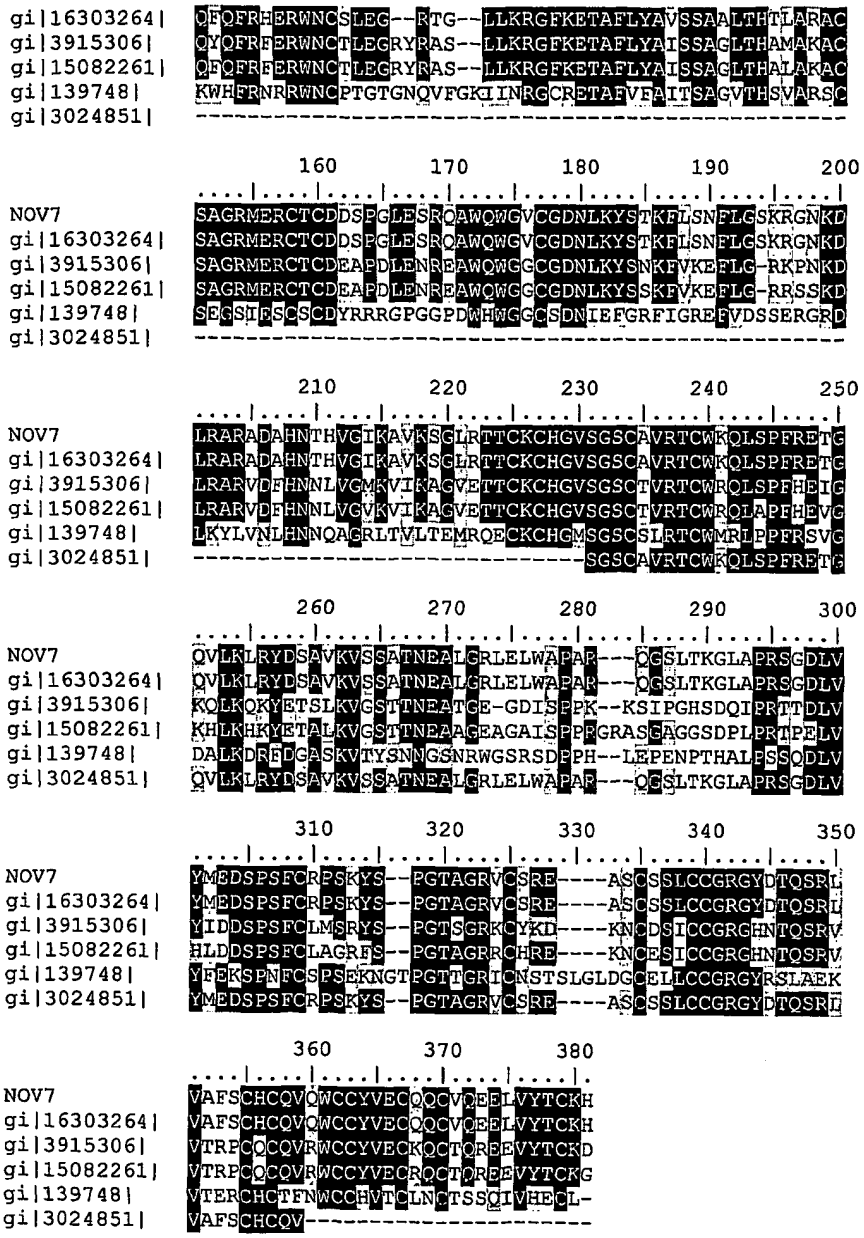
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|16303264|dbj|BAB70499.1| (AB063483)	WNT14B [Homo sapiens]	357	330/331 (99%)	330/331 (99%)	e-175
gi|3915306|sp|O42280|WN14_CHICK	WNT-14 PROTEIN PRECURSOR	354	204/332 (61%)	253/332 (75%)	e-109
gi|15082261|ref|NP_003386.1| (NM_003395)	wingless-type MMTV integration site family, member 14 [Homo sapiens]	365	209/335 (62%)	255/335 (75%)	e-108
gi|139748|sp|P10108|WNT1_XENLA	WNT-1 PROTEIN PRECURSOR (XWNT-1) (XINT-1)	371	120/313 (38%)	175/313 (55%)	5e-58
gi|3024851|sp|O14905|WN15_HUMAN	WNT-15 PROTEIN	120	120/120 (100%)	120/120 (100%)	2e-56

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 7D.

Table 7D Information for the ClustalW proteins

1) NOV7 (SEQ ID NO:20)
2) gi|16303264|dbj|BAB70499.1| (AB063483) WNT14B [Homo sapiens] (SEQ ID NO:62)
3) gi|3915306|sp|O42280|WN14_CHICK WNT-14 PROTEIN PRECURSOR (SEQ ID NO:63)
4) gi|15082261|ref|NP_003386.1| (NM_003395) wingless-type MMTV integration site family, member 14 [Homo sapiens] (SEQ ID NO:64)
5) gi|139748|sp|P10108|WNT1_XENLA WNT-1 PROTEIN PRECURSOR (XWNT-1) (XINT-1) (SEQ ID NO:65)
6) gi|3024851|sp|O14905|WN15_HUMAN WNT-15 PROTEIN (SEQ ID NO:66)





Tables 7E and 7F list the domain descriptions from DOMAIN analysis results against NOV7. This indicates that the NOV7 sequence has properties similar to those of other proteins known to contain this domain.

Table 7E. Domain Analysis of NOV7

gnl|Pfam|pfam00110, wnt, wnt family. (SEQ ID NO:104)
CD-Length = 313 residues, 97.8% aligned
Score = 268 bits (684), Expect = 5e-73

```
NOV 6:  34   LSRRQKQLCRREPGLAETLRDAAHLGLLECQFQFRHERWNCSLEGRMGL-----LKRGFK  88
             || ||+|||||  | +  ++ + | | + ||| |||  |||||   |+ +     ||+| +
Sbjct:  8    LSPRQRQLCRRNPDVMASVSEGAQLAIQECQHQFRGRRWNCSTLDRLRVVFGKVLKKGTR  67

NOV 6:  89   ETAFLYAVSSAALTHTLARACSAGRMERCTCDDSPG-LESRQAWQWGVCGDNLKYSTKFL  147
             ||||+||+||| + | + |||| | +| | ||   |    + +|||| | ||+++  +|
Sbjct:  68   ETAFVYAISSAGVAHAVTRACSEGELESCGCDYKKGPGGPQGSWQWGGCSDNVEFGIRFS  127

NOV 6:  148  SNFLGSKRGNKDLRARADAHNTHVGIKAVKSGLRTTCKCHGVSGSCAVRTCWKQLSPFRE  207
               |+ ++   +| |+  + ||   | ||||| +|  ||||||||||+++|||  |  ||
Sbjct:  128  REFVDARERERDARSLMNLHNNEAGRKAVKSHMRRECKCHGVSGSCSMKTCWLSLPDFRA  187

NOV 6:  208  TGQVLKLRYDSAVKVSSATNEALGRLELWAPARQGSLTKGLAPRSGDLVYMEDSPSFCR-  266
              |  || +|| |++|        | + ||       +   |   ||||+|||| +|
Sbjct:  188  VGDALKDKYDGAIRV---EPNKRGMGQGSAPRLVAKNPRFKPPTRSDLVYLEDSPDYCER  244

NOV 6:  267  -PSKYSPGTAGRVCSREA----SCSSLCCGRGYDTQSRLVAFSCHCQVQWCCYVECQQCV  321
               |  | || ||||++ +     |  |||||||+||       |+|+  |||||+|++|
Sbjct:  245  DRSTGSLGTQGRVCNKTSKGLDGCELLCCGRGYNTQQVERTEKCNCKFHWCCYVKCEECQ  304

NOV 6:  322  QEELVYTCK  330
             +   |+|||
Sbjct:  305  EVVEVHTCK  313
```

Table 7F. Domain Analysis of NOV7

gnl|Smart|smart00097, WNT1, found in Wnt-1 (SEQ ID NO:105)
CD-Length = 304 residues, 98.7% aligned
Score = 248 bits (632), Expect = 5e-67

```
NOV 6:  34   LSRRQKQLCRREPGLAETLRDAAHLGLLECQFQFRHERWNCSLEGRMGL----LKRGFKE  89
             |||||+||||  | +  ++ + |  |+ ||| |||  |||||  |   +    |++| +|
Sbjct:  5    LSRRQRQLCRANPDVMASVAEGAQEGIEECQHQFRFRRWNCSTAGLASIFGKVLRQGTRE  64

NOV 6:  90   TAFLYAVSSAALTHTLARACSAGRMERCTCDDSPGLESRQAWQWGVCGDNLKYSTKFLSN  149
             |||+||+|||| + | + |||| | ++ | || |      + |+|| | ||+ +   |
Sbjct:  65   TAFVYAISSAGVAHAVTRACSQGELDSCGCDYSKRGSGGRGWEWGGCSDNIDFGIGFSRE  124

NOV 6:  150  FLGSK-RGNKDLRARADAHNTHVGIKAVKSGLRTTCKCHGVSGSCAVRTCWKQLSPFRET  208
             |+ ++ |   | ||  + ||   |  |||  ++  ||||||||||+|+|||  ||  |||
Sbjct:  125  FVDARERRGSDARALMNLHNNEAGRLAVKKTMKRECKCHGVSGSCSVKTCWLQLPEFREI  184

NOV 6:  209  GQVLKLRYDSAVKVSSATNEALGRLELWAPARQGSLTKGLAPRSGDLVYMEDSPSFC--R  266
             |  || +|| | +|          |       +         | + ||||+|  ||  ||
Sbjct:  185  GDYLKEKYDGASEV-VLDKRGTRGLVPANRDFK--------PPTNTDLVYLESSPDFCEKN  236

NOV 6:  267  PSKYSPGTAGRVCSREA----SCSSLCCGRGYDTQSRLVAFSCHCQVQWCCYVECQQCVQ  322
             |   | || ||||++ +     |  |||||||+|+   |   |+|+  |||||+|+|| +
Sbjct:  237  PKTGSLGTQGRVCNKTSKGLDGCDLLCCGRGYNTEHVEVVERCNCKFHWCCYVKCKQCRE  296

NOV 6:  323  EELVYTCK  330
                +|||
Sbjct:  297  RVEKHTCK  304
```

Wnt proteins constitute a large family of molecules involved in cell proliferation, cell differentiation and embryonic patterning. They are known to interact with the Frizzled family of receptors to activate two main intracellular signaling pathways regulating intracellular calcium levels and gene transcription. Early studies on Wnts implicated them in cell proliferation and tumorigenesis, which have been borne out by recent work using transgenic

and null mutant mice. Wnts are involved in processes involved in mammary gland development and cancer. Recent studies have demonstrated that these molecules are critical to organogenesis of several systems, such as the kidney and brain. Wnts regulate the early development, i.e. neural induction, and their role persists in later stages of development as well as in the mature organ. An example of this is seen in the brain, where the loss of certain Wnts leads to the absence of critical regions of the brain, e.g. the hippocampus, involved in learning and memory, or the cerebellum, involved in motor function. Wnts have also been implicated in the genesis of degenerative diseases such as Alzheimer's disease. The protein encoded by the novel gene described herein may therefore play a role in cellular proliferation, differentiation, dysregulation, organogenesis and disease processes such as cancer, developmental defects etc.

A partial sequence corresponding to this novel protein, with homology to the chicken Wnt-14, has been deposited in GenBank with the nomenclature Wnt-15.

Alzheimer's disease (AD) is a neurodegenerative disease with progressive dementia accompanied by three main structural changes in the brain: diffuse loss of neurons; intracellular protein deposits termed neurofibrillary tangles (NFT) and extracellular protein deposits termed amyloid or senile plaques, surrounded by dystrophic neurites. Two major hypotheses have been proposed in order to explain the molecular hallmarks of the disease: The 'amyloid cascade' hypothesis and the 'neuronal cytoskeletal degeneration' hypothesis. While the former is supported by genetic studies of the early-onset familial forms of AD (FAD), the latter revolves around the observation in vivo that cytoskeletal changes - including the abnormal phosphorylation state of the microtubule associated protein tau - may precede the deposition of senile plaques. Recent studies have suggested that the trafficking process of membrane associated proteins is modulated by the FAD-linked presenilin (PS) proteins, and that amyloid beta-peptide deposition may be initiated intracellularly, through the secretory pathway. Current hypotheses concerning presenilin function are based upon its cellular localization and its putative interaction as macromolecular complexes with the cell-adhesion/signaling beta-catenin molecule and the glycogen synthase kinase 3beta (GSK-3beta) enzyme. Developmental studies have shown that PS proteins function as components in the Notch signal transduction cascade and that beta-catenin and GSK-3beta are transducers of the Wnt signaling pathway. Both pathways are thought to have an important role in brain development, and they have been connected through Dishevelled (Dvl) protein, a known transducer of the Wnt pathway.

Members of the vertebrate Wnt family have been subdivided into two functional classes according to their biological activities. Some Wnts signal through the canonical Wnt-1/wingless pathway by stabilizing cytoplasmic beta-catenin. By contrast other Wnts stimulate intracellular Ca2+ release and activate two kinases, CamKII and PKC, in a G-protein-dependent manner. Moreover, putative Wnt receptors belonging to the Frizzled gene family have been identified that preferentially couple to the two prospective pathways in the absence of ectopic Wnt ligand and that might account for the signaling specificity of the Wnt pathways. As Ca2+ release was the first described feature of the noncanonical pathway, and as Ca2+ probably plays a key role in the activation of CamKII and PKC, Kuhl M, et al., (*Trends Genet* 2000 Jul;16(7):279-83) have named this Wnt pathway the Wnt/Ca2+ pathway.

Many constituents of Wnt signaling pathways are expressed in the developing and mature nervous systems. Recent work has shown that Wnt signaling controls initial formation of the neural plate and many subsequent patterning decisions in the embryonic nervous system, including formation of the neural crest. Wnt signaling continues to be important at later stages of development. Wnts have been shown to regulate the anatomy of the neuronal cytoskeleton and the differentiation of synapses in the cerebellum. Wnt signaling has been demonstrated to regulate apoptosis and may participate in degenerative processes leading to cell death in the aging brain.

Recent genetic studies have shown that the signalling factor Wnt3a is required for formation of the hippocampus; the developmental consequences of Wnt signalling in the hippocampus are mediated by multiple HMG-box transcription factors, with LEF-1 being required just for formation of the dentate gyrus.

Wnt-1 was first identified as a protooncogene activated by viral insertion in mouse mammary tumors. Transgenic expression of this gene using a mouse mammary tumor virus LTR enhancer causes extensive ductal hyperplasia early in life and mammary adenocarcinomas in approximately 50% of the female transgenic (TG) mice by 6 months of age. Metastasis to the lung and proximal lymph nodes is rare at the time tumors are detected but frequent after the removal of the primary neoplasm. The potent mitogenic effect mediated by Wnt-1 expression does not require estrogen stimulation; tumors form after an increased latency in estrogen receptor alpha-null mice. Several genetic lesions, including inactivation of p53 and over-expression of Fgf-3, collaborate with Wnt-1 in leading to mammary tumors, but loss of Sky and inactivation of one allele of Rb do not affect the rate of tumor formation in Wnt-1 TG mice.

Communication between cells is often mediated by secreted signaling molecules that bind cell surface receptors and modulate the activity of specific intracellular effectors. The Wnt family of secreted glycoproteins is one group of signaling molecules that has been shown to control a variety of developmental processes including cell fate specification, cell proliferation, cell polarity and cell migration. In addition, mis-regulation of Wnt signaling can cause developmental defects and is implicated in the genesis of several human cancers. The importance of Wnt signaling in development and in clinical pathologies is underscored by the large number of primary research papers examining various aspects of Wnt signaling that have been published in the past several years.

Reproductive tract development and function is regulated by circulating steroid hormones. In the mammalian female reproductive tract, estrogenic compounds direct many aspects of cytodifferentiation including uterine gland formation, smooth muscle morphology, and epithelial differentiation. While it is clear that these hormones act through their cognate nuclear receptors, it is less clear what signaling events follow hormonal stimulation that govern cytodifferentiation. Recent advances in molecular embryology and cancer cell biology have identified the Wnt family of secreted signaling molecules. Discussed here are recent advances that point to a definitive role during uterine development and adult function for one member of the Wnt gene family, Wnt-7a. In addition, recent data is reviewed that implicates Wnt-7a deregulation in response to pre-natal exposure to the synthetic estrogenic compound, DES. These advances point to an important role for the Wnt gene family in various reproductive tract pathologies including cancer.

Holoprosencephaly (HPE) is the most common developmental defect of the forebrain in humans. Several distinct human genes for holoprosencephaly have now been identified. They include Sonic hedgehog (SHH), ZIC2, and SIX3. Many additional genes involved in forebrain development are rapidly being cloned and characterized in model vertebrate organisms. These include Patched (Ptc), Smoothened (Smo), cubitus interuptus (ci)/Gli, wingless (wg/Wnt, decapentaplegic (dpp)/BMP, Hedgehog interacting protein (Hip), nodal, Smads, One-eyed pinhead (Oep), and TG-Interacting Factor (TGIF). However, further analysis is needed before their roles in HPE can be established.

Female reproductive hormones control mammary gland morphogenesis. In the absence of the progesterone receptor (PR) from the mammary epithelium, ductal side-branching fails to occur. Brisken C, et al. (*Genes Dev* 2000 Mar 15;14(6):650-4) overcame this defect by ectopic expression of the protooncogene Wnt-1. Transplantation of mammary epithelia from Wnt-4(-)/(-) mice shows that Wnt-4 has an essential role in side-branching early in pregnancy. PR and

Wnt-4 mRNAs colocalize to the luminal compartment of the ductal epithelium. Progesterone induces Wnt-4 in mammary epithelial cells and is required for increased Wnt-4 expression during pregnancy. Thus, Wnt signaling is essential in mediating progesterone function during mammary gland morphogenesis.

Synapse formation requires changes in cell morphology and the upregulation and localization of synaptic proteins. In the cerebellum, mossy fibers undergo extensive remodeling as they contact several granule cells and form complex, multisynaptic glomerular rosettes. Hall AC, et al., (*Cell* 2000 Mar 3;100(5):525-35) showed that granule cells secrete factors that induce axon and growth cone remodeling in mossy fibers. This effect is blocked by the WNT antagonist, sFRP-1, and mimicked by WNT-7a, which is expressed by granule cells. WNT-7a also induces synapsin I clustering at remodeled areas of mossy fibers, a preliminary step in synaptogenesis. Wnt-7a mutant mice show a delay in the morphological maturation of glomerular rosettes and in the accumulation of synapsin I. We propose that WNT-7a can function as a synaptogenic factor.

Estrogens have important functions in mammary gland development and carcinogenesis. To better define these roles, Bocchinfuso WP, et al., (*Cancer Res* 1999 Apr 15;59(8):1869-76) have used two previously characterized lines of genetically altered mice: estrogen receptor-alpha (ER alpha) knockout (ERKO) mice, which lack the gene encoding ER alpha, and mouse mammary virus tumor (MMTV)-Wnt-1 transgenic mice (Wnt-1 TG), which develop mammary hyperplasia and neoplasia due to ectopic production of the Wnt-1 secretory glycoprotein. Bocchinfuso WP, et al. have crossed these lines to ascertain the effects of ER alpha deficiency on mammary gland development and carcinogenesis in mice expressing the Wnt-1 transgene. Introduction of the Wnt-1 transgene into the ERKO background stimulates proliferation of alveolar-like epithelium, indicating that Wnt-1 protein can promote mitogenesis in the absence of an ER alpha-mediated response. The hyperplastic glandular tissue remains confined to the nipple region, implying that the requirement for ER alpha in ductal expansion is not overcome by ectopic Wnt-1. Tumors were detected in virgin ERKO females expressing the Wnt-1 transgene at an average age (48 weeks) that is twice that seen in virgin Wnt-1 TG mice (24 weeks) competent to produce ER alpha. Prepubertal ovariectomy of Wnt-1 TG mice also extended tumor latency to 42 weeks. However, pregnancy did not appear to accelerate the appearance of tumors in Wnt-1 TG mice, and tumor growth rates were not measurably affected by late ovariectomy. Small hyperplastic mammary glands were observed in Wnt-1 TG males, regardless of ER alpha gene status; the glands were similar in appearance to those found in ERKO/Wnt-1 TG females. Mammary tumors also occurred in Wnt-1 TG

males; latency tended to be longer in the heterozygous ER alpha and ERKO males (86 to 100 weeks) than in wild-type ER alpha mice (ca. 75 weeks). Bocchinfuso WP, et al. concluded that ectopic expression of the Wnt-1 proto-oncogene can induce mammary hyperplasia and tumorigenesis in the absence of ER alpha in female and male mice. The delayed time of tumor appearance may depend on the number of cells at risk of secondary events in the hyperplastic glands, on the carcinogenesis-promoting effects of ER alpha signaling, or on both.

Wnt-1 and Wnt-3a proto-oncogenes have been implicated in the development of midbrain and hindbrain structures. Evidence for such a role has been derived from in situ hybridization studies showing Wnt-1 and -3a expression in developing cranial and spinal cord regions and from studies of mutant mice whose Wnt-1 genes have undergone targeted disruption by homologous recombination. Wnt-1 null mutants exhibit cranial defects but no spinal cord abnormalities, despite expression of the gene in these regions. The absence of spinal cord abnormalities is thought to be due to a functional compensation of the Wnt-1 deficiency by related genes, a problem that has complicated the analysis of null mutants of other developmental genes as well. Augustine K, et al., (*Dev Genet* 1993;14(6):500-20) describe the attenuation of Wnt-1 expression using antisense oligonucleotide inhibition in mouse embryos grown in culture. Augustine K, et al. induced similar mid- and hindbrain abnormalities as those seen in the Wnt-1 null mutant mice. Attenuation of Wnt-1 expression was also associated with cardiomegaly resulting in hemostasis. These findings are consistent with the possibility that a subset of Wnt-1 expressing cells include neural crest cells known to contribute to septation of the truncus arteriosus and to formation of the visceral arches. Antisense knockout of Wnt-3a, a gene structurally related to Wnt-1, targeted the forebrain and midbrain region, which were hypoplastic and failed to expand, and the spinal cord, which exhibited lateral outpocketings at the level of the forelimb buds. Dual antisense knockouts of Wnt-1 and Wnt-3a targeted all brain regions leading to incomplete closure of the cranial neural folds, and an increase in the number and severity of outpocketings along the spinal cord, suggesting that these genes complement one another to produce normal patterning of the spinal cord. The short time required to assess the mutant phenotype (2 days) and the need for limited sequence information of the target gene (20-25 nucleotides) make this antisense oligonucleotide/whole embryo culture system ideal for testing the importance of specific genes and their interactions in murine embryonic development.

Wnt-1 (previously known as int-1) is a proto-oncogene induced by the integration of the mouse mammary tumor virus. It is thought to play a role in intercellular communication and seems to be a signalling molecule important in the development of the central nervous

system (CNS). The sequence of wnt-1 is highly conserved in mammals, fish, and amphibians. Wnt-1 is a member of a large family of related proteins that are all thought to be developmental regulators. These proteins are known as wnt-2 (also known as irp), wnt-3 up to wnt-15. At least four members of this family are present in Drosophila. One of them, wingless (wg), is implicated in segmentation polarity. All these proteins share the following features characteristics of secretory proteins, a signal peptide, several potential N-glycosylation sites and 22 conserved cysteines that are probably involved in disulfide bonds. The Wnt proteins seem to adhere to the plasma membrane of the secreting cells and are therefore likely tosignal over only few cell diameters.

The disclosed NOV7 nucleic acid of the invention encoding a Wnt-15-like protein includes the nucleic acid whose sequence is provided in Table 7A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 7A while still encoding a protein that maintains its Wnt-15-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 32 percent of the bases may be so changed.

The disclosed NOV7 protein of the invention includes the Wnt-15-like protein whose sequence is provided in Table 7B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 7B while still encoding a protein that maintains its Wnt-15-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 38 percent of the residues may be so changed.

The above defined information for this invention suggests that these Wnt-15-like proteins (NOV7) may function as a member of a "Wnt-15 family". Therefore, the NOV7 nucleic acids and proteins identified here may be useful in potential therapeutic applications

implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The nucleic acids and proteins of NOV7 are useful in Von Hippel-Lindau (VHL) syndrome , Alzheimer's disease, stroke, tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies and disorders. The novel NOV7 nucleic acid encoding NOV7 protein,, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

NOV7 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV7 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV7 epitope is from about amino acids 25 to 60. In other embodiments, NOV7 epitope is from about amino acids 65 to 80, from about amino acids 110 to 140, from about amino acids 145 to 180, from about amino acids 190 to 220, from about amino acids 230 to 270, or from about amino acids 280 to 290. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV8

A disclosed NOV8 nucleic acid of 1085 nucleotides (also referred to 88091010_EXT) encoding a novel Wnt-14-like protein is shown in Table 8A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 13-15 and ending with a

TGA codon at nucleotides 1078-1080. In Table 8A, the 5' and 3' untranslated regions are underlined and the start and stop codons are in bold letters.

Table 8A. NOV8 Nucleotide Sequence (SEQ ID NO:21)

TAGTGAGCCGAGATGGCACTACTATATTCCAGCTTGGGTGTGGTTGTGTGCACCTGTAGTCCTAGTTACTT
TGGACTGACGGGCAGCGAGCCCCTGACCATCCTCCCGCTGACCCTGGAGCCAGAGGCGGCTGCCCAGGCGC
ACTACAAGGCCTGCGACCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCCGCCGGGACCCGGGCGTG
GCAGAGACGCTGGTGGAGGCCGTGAGCATGAGTGCGCTCGAGTGCCAGTTCCAGTTCCGCTTTGAGCGCTG
GAACTGCACGCTGGAGGGCCGCTACCGGGCCAGCCTGCTCAAGCGAGGTTTCAAGGAGACTGCCTTCCTCT
ATGCCATCTCCTCGGCTGGCCTGACGCACGCACTGGCCAAGGCGTGCAGCGCGGGCCGCATGGAGCGCTGT
ACCTGCGATGAGGCACCCGACCTGGAGAACCGTGAGGGCTGGAAGTGGGGTGGCTGTAGCGAGGACATCGA
GTTTGGTGGGATGGTGTCTCGGGAGTTCGCCGACGCCCGGGAGAACCGGCCAGATGCCCGCTCAGCCATGA
ACCGCCACAACAACGAGGCTGGGCGCCAGGTGATCAAGGCTGGGGTGGAGACCACCTGCAAGTGCCACGGC
GTGTCAGGCTCATGCACGGTGCGGACCTGCTGGCGGCAGTTGGCGCCTTTCCATGAGGTGGGCAAGCATCT
GAAGCACAAGTATGAGTCGGCACTCAAGGTGGGCAGCACCACCAATGAAGCTGCCGGCGAGGCAGGTGCCA
TCTCCCCACCACGGGGCCGTGCCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCCGCACTCCAGAGCTGGTG
CACCTGGATGACTCGCCTAGCTTCTGCCTGGCTGGCCGCTTCTCCCCGGGCACCGCTGGCCGTAGGTGCCA
CCGTGAGAAGAACTGCGAGAGCATCTGCTGTGGCCGCGGCCATAACACACAGAGCCGGGTGGTGACAAGGC
CCTGCCAGTGCCAGGTGCGTTGGTGCTGCTATGTGGAGTGCAGGCAGTGCACGCAGCGTGAGGAGGTCTAC
ACCTGCAAGGGCTGAGTTCC

The disclosed NOV8 nucleic acid sequence, localized to chromosome 1, has 560 of 725 bases (77%) identical to a gb:GENBANK-ID:AF031168|acc:AF031168.1 mRNA from *Gallus gallus* (*Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds ($E = 5.2e^{-115}$).

A disclosed NOV8 polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 355 amino acid residues and is presented using the one-letter amino acid code in Table 8B. Signal P, Psort and/or Hydropathy results predict that NOV8 has a signal peptide and is likely to be localized extracellularly with a certainty of 0.3700. In other embodiments, NOV8 is also likely to be localized to the enoplasmic reticulum (membrane) with a certainty of 0.1000, to the endoplasmic reticulum (lumen) with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000. The most likely cleavage site for a NOV8 peptide is between amino acids 15 and 16, at: CTC-SP.

Table 8B. Encoded NOV8 protein sequence (SEQ ID NO:22).

MALLYSSLGVVVCTCSPSYFGLTGSEPLTILPLTLEPEAAAQAHYKACDRLKLERKQRRMCRRDPGVAETL
VEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFKETAFLYAISSAGLTHALAKACSAGRMERCTCDE
APDLENREGWKWGGCSEDIEFGGMVSREFADARENRPDARSAMNRHNNEAGRQVIKAGVETTCKCHGVSGS
CTVRTCWRQLAPFHEVGKHLKHKYESALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDD
SPSFCLAGRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEVYTCKG

The disclosed NOV8 amino acid sequence has 270 of 354 amino acid residues (76%) identical to, and 310 of 354 amino acid residues (87%) similar to, the 354 amino acid residue ptnr:SWISSPROT-ACC:O42280 protein from *Gallus gallus* (Chicken) (WNT-14 Protein Precursor ($1.2e^{-151}$).

NOV8 is expressed in at least brain. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

In addition, the sequence is predicted to be expressed in brain because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF031168|acc:AF031168.1) a closely related [*Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds].

NOV8 also has homology to the amino acid sequence shown in the BLASTP data listed in Table 8C.

Table 8C. BLAST results for NOV8

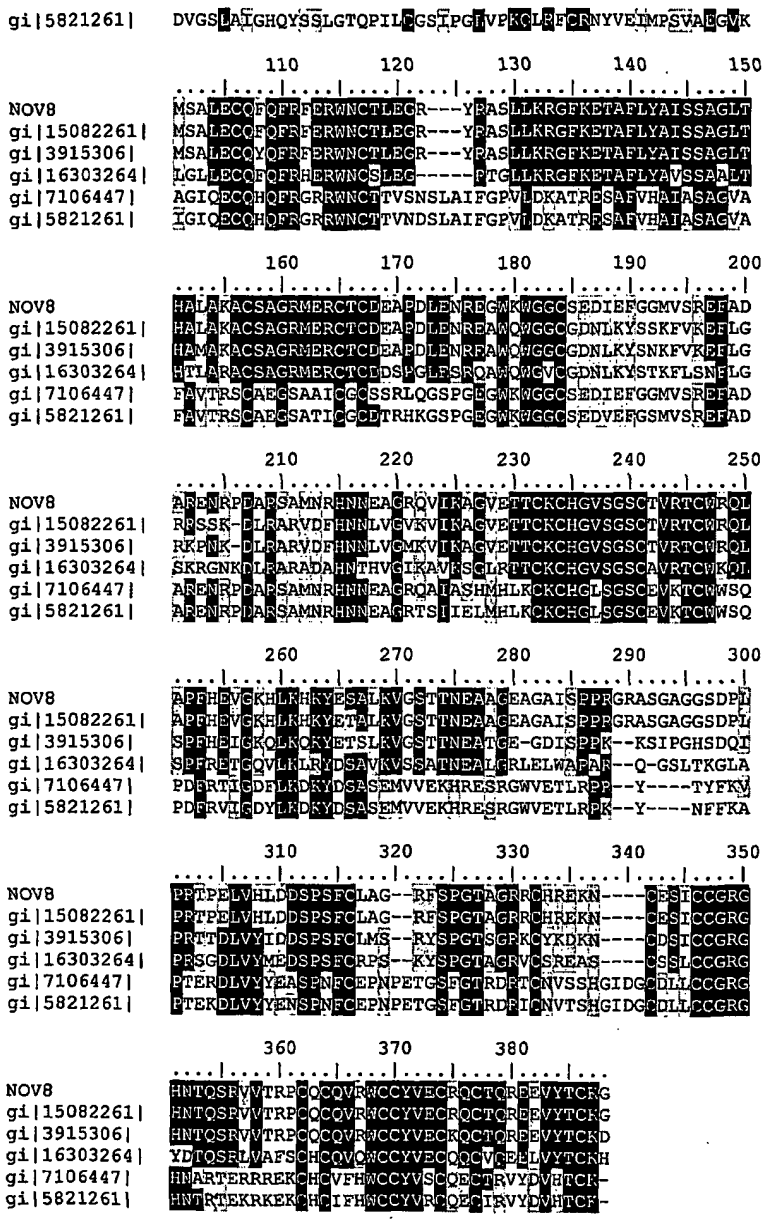
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi|15082261|ref|NP_003386.1| (NM_003395)	wingless-type MMTV integration site family, member 14 [Homo sapiens]	365	306/340 (90%)	321/340 (94%)	e-167
gi|3915306|sp|O42280|WN14_CHICK	WNT-14 PROTEIN PRECURSOR	354	270/357 (75%)	310/357 (86%)	e-142
gi|16303264|dbj|BAB70499.1| (AB063483)	WNT14B [Homo sapiens]	357	193/339 (56%)	244/339 (71%)	e-100
gi|7106447|ref|NP_033548.1| (NM_009522)	wingless-related MMTV integration site 3A [Mus musculus]	352	141/311 (45%)	179/311 (57%)	2e-62
gi|5821261|dbj|BAA83743.1| (AB024080)	Wnt-3a [Gallus gallus]	376	139/311 (44%)	179/311 (56%)	3e-62

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 8D.

Table 8D. Information for the ClustalW proteins

1) NOV8 (SEQ ID NO:22)
2) gi|15082261|ref|NP_003386.1| (NM_003395) wingless-type MMTV integration site family, member 14 [Homo sapiens] (SEQ ID NO:64)
3) gi|3915306|sp|O42280|WN14_CHICK WNT-14 PROTEIN PRECURSOR (SEQ ID NO:63)
4) gi|16303264|dbj|BAB70499.1| (AB063483) WNT14B [Homo sapiens] (SEQ ID NO:62)
5) gi|7106447|ref|NP_033548.1| (NM_009522) wingless-related MMTV integration site 3A [Mus musculus] (SEQ ID NO:67)
6) gi|5821261|dbj|BAA83743.1| (AB024080) Wnt-3a [Gallus gallus] (SEQ ID NO:68)

```
                    10        20        30        40        50
                    ....|....|....|....|....|....|....|....|....|....|
NOV8                ----------MALLYSSLGVVVCT-----CSPSYFGLTGSEPLTILP--
gi|15082261|        MLDGSPLARWLAAAFGLTLLLAALR-----PSAAYFGLTGSEPLTILP--
gi|3915306|         ----------MALLRALGLLACTP---RPSAAYFGLTGNEALTILP--
gi|16303264|        -------MRPPPALALAGLCLLALP----AAAASYFGLTGREVLTPFPG-
gi|7106447|         -----MAPLGYLLVLCS---LKQA-------LG-SYPIWWS---------
gi|5821261|         -----MKSFCSEVVAKSRLGLKQWGWCGWTPMGSAWKKWISEQRSSLELW

                    60        70        80        90        100
                    ....|....|....|....|....|....|....|....|....|....|
NOV8                ----LTLEP-EAAAQAHYNACDRLK-LERKQRRMCRRDPGVAETLVEAVS
gi|15082261|        ----LTLEP-EAAAQAHYNACDRLK-LERKQRRMCRRDPGVAETLVEAVS
gi|3915306|         ----LTSEMEEAAVKAHYNVCDRLK-LEKKQRRMCRRDPGGAETLMEALS
gi|16303264|        ----LGTAAAPAQGGAHLNCCDLLK-LSRRQKQLCRREPGLAETLRDAAH
gi|7106447|         ----LAVGPQYSSLSTQPILQASIPGLVPKQLRFCPNYVEIMPSVAEGVK
```



Tables 8E and 8F list the domain descriptions from DOMAIN analysis results against NOV8. This indicates that the NOV8 sequence has properties similar to those of other proteins known to contain this domain.

Table 8E. Domain Analysis of NOV8

gnl|Pfam|pfam00110, wnt, wnt family. (SEQ ID NO:104)
CD-Length = 313 residues, 99.7% aligned
Score = 313 bits (801), Expect = 1e-86

```
NOV 7:   48   CDRLK-LERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASL---  103
              |  |  |  +||++|||+| |  ++ |   ++  ||| |||  ||||+   | |
Sbjct:   2    CRSLPGLSPRQRQLCRRNPDVMASVSEGAQLAIQECQHQFRGRRWNCSTLDRLRVVFGKV  61

NOV 7:   104  LKRGFKETAFLYAISSAGLTHALAKACSAGRMERCTCDE-APDLENREGWKWGGCSEDIE  162
              ||+| +||||+|||||||+ ||+ +||| | +| | ||        +  |+|||||+++|
Sbjct:   62   LKKGTRETAFVYAISSAGVAHAVTRACSEGELESCGCDYKKGPGGPQGSWQWGGCSDNVE  121

NOV 7:   163  FGGMVSREFADARENRPDARSAMNRHNNEAGRQVIKAGVETTCKCHGVSGSCTVRTCWRQ  222
              ||   |||| ||||   |||| || |||||||+ +|+ +   ||||||||||+++|||
Sbjct:   122  FGIRFSREFVDARERERDARSLMNLHNNEAGRKAVKSHMRRECKCHGVSGSCSMKTCWLS  181

NOV 7:   223  LAPFHEVGKHLKHKYESALKV-GSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVH  281
              |  |  ||  || ||+ |++|  +      | |  +     |       ||       ||+
Sbjct:   182  LPDFRAVGDALKDKYDGAIRVEPNKRGMGQGSAPRLVAKNPRFKPPTRSD-------LVY  234

NOV 7:   282  LDDSPSFCL--AGRFSPGTAGRRC----HREKNCESICCGRGHNTQSRVVTRPCQCQVRW  335
              |+||| +|       | || || |         || +|||||+|||    |  | |+  |
Sbjct:   235  LEDSPDYCERDRSTGSLGTQGRVCNKTSKGLDGCELLCCGRGYNTQQVERTEKCNCKFHW  294

NOV 7:   336  CCYVECRQCTQREEVYTCK  354
              ||||+| +| +  ||+|||
Sbjct:   295  CCYVKCEECQEVVEVHTCK  313
```

Table 8F. Domain Analysis of NOV8

gnl|Smart|smart00097, WNT1, found in Wnt-1 (SEQ ID NO:105)
CD-Length = 304 residues, 98.7% aligned
Score = 292 bits (748), Expect = 2e-80

```
NOV 7:   53   LERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRA--SLLKRGFKE  110
              | |+||++|| +| |  ++ |       ||| |||| ||||+  |       +|++| +|
Sbjct:   5    LSRRQRQLCRANPDVMASVAEGAQEGIEECQHQFRFRRWNCSTAGLASIFGKVLRQGTRE  64

NOV 7:   111  TAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREGWKWGGCSEDIEFGGMVSRE  170
              |||+|||||||+ ||+ +||| | ++ | || +       ||+|||||++|+||   |||
Sbjct:   65   TAFVYAISSAGVAHAVTRACSQGELDSCGCDYSKRGSGGRGWEWGGCSDNIDFGIGFSRE  124

NOV 7:   171  FADARENR-PDARSAMNRHNNEAGRQVIKAGVETTCKCHGVSGSCTVRTCWRQLAPFHEV  229
              | |||| |  |||+ || |||||||  +|  ++  ||||||||||+|+|+||| ||  | |+
Sbjct:   125  FVDARERRGSDARALMNLHNNEAGRLAVKKTMKRECKCHGVSGSCSVKTCWLQLPEFREI  184

NOV 7:   230  GKHLKHKYESALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFC  289
              | +|| ||+ | +|                          |       |   +||+|+ || ||
Sbjct:   185  GDYLKEKYDGASEVVLD-----------KRGTRGLVPANRDFKPPTNTDLVYLESSPDFC  233

NOV 7:   290  LAGRF--SPGTAGRRCHREKN----CESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQ  343
                     | || || |++       |+ +|||||+||+   |    | |+  |||||+|+|
Sbjct:   234  EKNPKTGSLGTQGRVCNKTSKGLDGCDLLCCGRGYNTEHVEVVERCNCKFHWCCYVKCKQ  293

NOV 7:   344  CTQREEVYTCK  354
              | +| | +|||
Sbjct:   294  CRERVEKHTCK  304
```

Wnt proteins constitute a large family of molecules involved in cell proliferation, cell differentiation and embryonic patterning. They are known to interact with the Frizzled family of receptors to activate two main intracellular signaling pathways regulating intracellular calcium levels and gene transcription. Early studies on Wnts implicated them in cell proliferation and tumorigenesis, which have been borne out by recent work using transgenic

and null mutant mice. Wnts are involved in processes involved in mammary gland development and cancer. Recent studies have demonstrated that these molecules are critical to organogenesis of several systems, such as the kidney and brain. Wnts regulate the early development, i.e. neural induction, and their role persists in later stages of development as well as in the mature organ. An example of this is seen in the brain, where the loss of certain Wnts leads to the absence of critical regions of the brain, e.g. the hippocampus, involved in learning and memory, or the cerebellum, involved in motor function. Wnts have also been implicated in the genesis of degenerative diseases such as Alzheimer's disease. The protein encoded by the novel gene described herein may therefore play a role in cellular proliferation, differentiation, dysregulation, organogenesis and disease processes such as cancer, developmental defects etc.

Alzheimer's disease (AD) is a neurodegenerative disease with progressive dementia accompanied by three main structural changes in the brain: diffuse loss of neurons; intracellular protein deposits termed neurofibrillary tangles (NFT) and extracellular protein deposits termed amyloid or senile plaques, surrounded by dystrophic neurites. Two major hypotheses have been proposed in order to explain the molecular hallmarks of the disease: The 'amyloid cascade' hypothesis and the 'neuronal cytoskeletal degeneration' hypothesis. While the former is supported by genetic studies of the early-onset familial forms of AD (FAD), the latter revolves around the observation in vivo that cytoskeletal changes - including the abnormal phosphorylation state of the microtubule associated protein tau - may precede the deposition of senile plaques. Recent studies have suggested that the trafficking process of membrane associated proteins is modulated by the FAD-linked presenilin (PS) proteins, and that amyloid beta-peptide deposition may be initiated intracellularly, through the secretory pathway. Current hypotheses concerning presenilin function are based upon its cellular localization and its putative interaction as macromolecular complexes with the cell-adhesion/signaling beta-catenin molecule and the glycogen synthase kinase 3beta (GSK-3beta) enzyme. Developmental studies have shown that PS proteins function as components in the Notch signal transduction cascade and that beta-catenin and GSK-3beta are transducers of the Wnt signaling pathway. Both pathways are thought to have an important role in brain development, and they have been connected through Dishevelled (Dvl) protein, a known transducer of the Wnt pathway.

Members of the vertebrate Wnt family have been subdivided into two functional classes according to their biological activities. Some Wnts signal through the canonical Wnt-1/wingless pathway by stabilizing cytoplasmic beta-catenin. By contrast other Wnts stimulate

intracellular Ca2+ release and activate two kinases, CamKII and PKC, in a G-protein-dependent manner. Moreover, putative Wnt receptors belonging to the Frizzled gene family have been identified that preferentially couple to the two prospective pathways in the absence of ectopic Wnt ligand and that might account for the signaling specificity of the Wnt pathways. As Ca2+ release was the first described feature of the noncanonical pathway, and as Ca2+ probably plays a key role in the activation of CamKII and PKC, Kuhl M, et al., (*Trends Genet* 2000 Jul;16(7):279-83) have named this Wnt pathway the Wnt/Ca2+ pathway.

Many constituents of Wnt signaling pathways are expressed in the developing and mature nervous systems. Recent work has shown that Wnt signaling controls initial formation of the neural plate and many subsequent patterning decisions in the embryonic nervous system, including formation of the neural crest. Wnt signaling continues to be important at later stages of development. Wnts have been shown to regulate the anatomy of the neuronal cytoskeleton and the differentiation of synapses in the cerebellum. Wnt signaling has been demonstrated to regulate apoptosis and may participate in degenerative processes leading to cell death in the aging brain.

Recent genetic studies have shown that the signalling factor Wnt3a is required for formation of the hippocampus; the developmental consequences of Wnt signalling in the hippocampus are mediated by multiple HMG-box transcription factors, with LEF-1 being required just for formation of the dentate gyrus.

Wnt-1 was first identified as a protooncogene activated by viral insertion in mouse mammary tumors. Transgenic expression of this gene using a mouse mammary tumor virus LTR enhancer causes extensive ductal hyperplasia early in life and mammary adenocarcinomas in approximately 50% of the female transgenic (TG) mice by 6 months of age. Metastasis to the lung and proximal lymph nodes is rare at the time tumors are detected but frequent after the removal of the primary neoplasm. The potent mitogenic effect mediated by Wnt-1 expression does not require estrogen stimulation; tumors form after an increased latency in estrogen receptor alpha-null mice. Several genetic lesions, including inactivation of p53 and over-expression of Fgf-3, collaborate with Wnt-1 in leading to mammary tumors, but loss of Sky and inactivation of one allele of Rb do not affect the rate of tumor formation in Wnt-1 TG mice.

Communication between cells is often mediated by secreted signaling molecules that bind cell surface receptors and modulate the activity of specific intracellular effectors. The Wnt family of secreted glycoproteins is one group of signaling molecules that has been shown to control a variety of developmental processes including cell fate specification, cell

proliferation, cell polarity and cell migration. In addition, mis-regulation of Wnt signaling can cause developmental defects and is implicated in the genesis of several human cancers. The importance of Wnt signaling in development and in clinical pathologies is underscored by the large number of primary research papers examining various aspects of Wnt signaling that have been published in the past several years.

Reproductive tract development and function is regulated by circulating steroid hormones. In the mammalian female reproductive tract, estrogenic compounds direct many aspects of cytodifferentiation including uterine gland formation, smooth muscle morphology, and epithelial differentiation. While it is clear that these hormones act through their cognate nuclear receptors, it is less clear what signaling events follow hormonal stimulation that govern cytodifferentiation. Recent advances in molecular embryology and cancer cell biology have identified the Wnt family of secreted signaling molecules. Discussed here are recent advances that point to a definitive role during uterine development and adult function for one member of the Wnt gene family, Wnt-7a. In addition, recent data is reviewed that implicates Wnt-7a deregulation in response to pre-natal exposure to the synthetic estrogenic compound, DES. These advances point to an important role for the Wnt gene family in various reproductive tract pathologies including cancer.

Holoprosencephaly (HPE) is the most common developmental defect of the forebrain in humans. Several distinct human genes for holoprosencephaly have now been identified. They include Sonic hedgehog (SHH), ZIC2, and SIX3. Many additional genes involved in forebrain development are rapidly being cloned and characterized in model vertebrate organisms. These include Patched (Ptc), Smoothened (Smo), cubitus interuptus (ci)/Gli, wingless (wg/Wnt, decapentaplegic (dpp)/BMP, Hedgehog interacting protein (Hip), nodal, Smads, One-eyed pinhead (Oep), and TG-Interacting Factor (TGIF). However, further analysis is needed before their roles in HPE can be established.

Female reproductive hormones control mammary gland morphogenesis. In the absence of the progesterone receptor (PR) from the mammary epithelium, ductal side-branching fails to occur. Brisken C, et al. (*Genes Dev* 2000 Mar 15;14(6):650-4) overcame this defect by ectopic expression of the protooncogene Wnt-1. Transplantation of mammary epithelia from Wnt-4(-)/(-) mice shows that Wnt-4 has an essential role in side-branching early in pregnancy. PR and Wnt-4 mRNAs colocalize to the luminal compartment of the ductal epithelium. Progesterone induces Wnt-4 in mammary epithelial cells and is required for increased Wnt-4 expression during pregnancy. Thus, Wnt signaling is essential in mediating progesterone function during mammary gland morphogenesis.

Synapse formation requires changes in cell morphology and the upregulation and localization of synaptic proteins. In the cerebellum, mossy fibers undergo extensive remodeling as they contact several granule cells and form complex, multisynaptic glomerular rosettes. Hall AC, et al., (*Cell* 2000 Mar 3;100(5):525-35) showed that granule cells secrete factors that induce axon and growth cone remodeling in mossy fibers. This effect is blocked by the WNT antagonist, sFRP-1, and mimicked by WNT-7a, which is expressed by granule cells. WNT-7a also induces synapsin I clustering at remodeled areas of mossy fibers, a preliminary step in synaptogenesis. Wnt-7a mutant mice show a delay in the morphological maturation of glomerular rosettes and in the accumulation of synapsin I. We propose that WNT-7a can function as a synaptogenic factor.

Estrogens have important functions in mammary gland development and carcinogenesis. To better define these roles, Bocchinfuso WP, et al., (*Cancer Res* 1999 Apr 15;59(8):1869-76) have used two previously characterized lines of genetically altered mice: estrogen receptor-alpha (ER alpha) knockout (ERKO) mice, which lack the gene encoding ER alpha, and mouse mammary virus tumor (MMTV)-Wnt-1 transgenic mice (Wnt-1 TG), which develop mammary hyperplasia and neoplasia due to ectopic production of the Wnt-1 secretory glycoprotein. Bocchinfuso WP, et al. have crossed these lines to ascertain the effects of ER alpha deficiency on mammary gland development and carcinogenesis in mice expressing the Wnt-1 transgene. Introduction of the Wnt-1 transgene into the ERKO background stimulates proliferation of alveolar-like epithelium, indicating that Wnt-1 protein can promote mitogenesis in the absence of an ER alpha-mediated response. The hyperplastic glandular tissue remains confined to the nipple region, implying that the requirement for ER alpha in ductal expansion is not overcome by ectopic Wnt-1. Tumors were detected in virgin ERKO females expressing the Wnt-1 transgene at an average age (48 weeks) that is twice that seen in virgin Wnt-1 TG mice (24 weeks) competent to produce ER alpha. Prepubertal ovariectomy of Wnt-1 TG mice also extended tumor latency to 42 weeks. However, pregnancy did not appear to accelerate the appearance of tumors in Wnt-1 TG mice, and tumor growth rates were not measurably affected by late ovariectomy. Small hyperplastic mammary glands were observed in Wnt-1 TG males, regardless of ER alpha gene status; the glands were similar in appearance to those found in ERKO/Wnt-1 TG females. Mammary tumors also occurred in Wnt-1 TG males; latency tended to be longer in the heterozygous ER alpha and ERKO males (86 to 100 weeks) than in wild-type ER alpha mice (ca. 75 weeks). Bocchinfuso WP, et al. concluded that ectopic expression of the Wnt-1 proto-oncogene can induce mammary hyperplasia and tumorigenesis in the absence of ER alpha in female and male mice. The delayed time of tumor

appearance may depend on the number of cells at risk of secondary events in the hyperplastic glands, on the carcinogenesis-promoting effects of ER alpha signaling, or on both.

Wnt-1 and Wnt-3a proto-oncogenes have been implicated in the development of midbrain and hindbrain structures. Evidence for such a role has been derived from in situ hybridization studies showing Wnt-1 and -3a expression in developing cranial and spinal cord regions and from studies of mutant mice whose Wnt-1 genes have undergone targeted disruption by homologous recombination. Wnt-1 null mutants exhibit cranial defects but no spinal cord abnormalities, despite expression of the gene in these regions. The absence of spinal cord abnormalities is thought to be due to a functional compensation of the Wnt-1 deficiency by related genes, a problem that has complicated the analysis of null mutants of other developmental genes as well. Augustine K, et al., (*Dev Genet* 1993;14(6):500-20) describe the attenuation of Wnt-1 expression using antisense oligonucleotide inhibition in mouse embryos grown in culture. Augustine K, et al. induced similar mid- and hindbrain abnormalities as those seen in the Wnt-1 null mutant mice. Attenuation of Wnt-1 expression was also associated with cardiomegaly resulting in hemostasis. These findings are consistent with the possibility that a subset of Wnt-1 expressing cells include neural crest cells known to contribute to septation of the truncus arteriosus and to formation of the visceral arches. Antisense knockout of Wnt-3a, a gene structurally related to Wnt-1, targeted the forebrain and midbrain region, which were hypoplastic and failed to expand, and the spinal cord, which exhibited lateral outpocketings at the level of the forelimb buds. Dual antisense knockouts of Wnt-1 and Wnt-3a targeted all brain regions leading to incomplete closure of the cranial neural folds, and an increase in the number and severity of outpocketings along the spinal cord, suggesting that these genes complement one another to produce normal patterning of the spinal cord. The short time required to assess the mutant phenotype (2 days) and the need for limited sequence information of the target gene (20-25 nucleotides) make this antisense oligonucleotide/whole embryo culture system ideal for testing the importance of specific genes and their interactions in murine embryonic development.

Wnt-1 (previously known as int-1) is a proto-oncogene induced by the integration of the mouse mammary tumor virus. It is thought to play a role in intercellular communication and seems to be a signalling molecule important in the development of the central nervous system (CNS). The sequence of wnt-1 is highly conserved in mammals, fish, and amphibians. Wnt-1 is a member of a large family of related proteins that are all thought to be developmental regulators. These proteins are known as wnt-2 (also known as irp), wnt-3 up to wnt-15. At least four members of this family are present in Drosophila. One of them, wingless

(wg), is implicated in segmentation polarity. All these proteins share the following features characteristics of secretory proteins, a signal peptide, several potential N-glycosylation sites and 22 conserved cysteines that are probably involved in disulfide bonds. The Wnt proteins seem to adhere to the plasma membrane of the secreting cells and are therefore likely tosignal over only few cell diameters.

The disclosed NOV8 nucleic acid of the invention encoding a Wnt-14-like protein includes the nucleic acid whose sequence is provided in Table 8A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 8A while still encoding a protein that maintains its Wnt-14-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 23 percent of the bases may be so changed.

The disclosed NOV8 protein of the invention includes the Wnt-14-like protein whose sequence is provided in Table 8B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 8B while still encoding a protein that maintains its Wnt-14-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 24 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the Wnt-14-like protein and nucleic acid (NOV8) disclosed herein suggest that NOV8 may have important structural and/or physiological functions characteristic of the Wnt-14-like family. Therefore, the NOV8 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic

applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV8 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering fromVon Hippel-Lindau (VHL) syndrome , Alzheimer's disease, stroke, tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies/disorders. The NOV8 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV8 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV8 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV8 epitope is from about amino acids 40 to 70. In another embodiment, the comtemplated NOV8 epitope is from about amino acids 80 to 110. In further embodiments, the contemplated NOV8 epitope is from about amino acids 120 to 200, from about amino acids 220 to 245, from about amino acids 250 to 280, or from about amino acids 290 to 340. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV9

A disclosed NOV9 nucleic acid of 2037 nucleotides (also referred to as AC069250_28_da1) encoding a beta-adrenergic receptor kinase-like protein is shown in Table 9A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 16-18 and ending with a TGA codon at nucleotides 2020-2022. A putative untranslated region upstream from the initiation codon and downstream from the termination

codon is underlined in Table 9A. The start and stop codons are in bold letters. Single nucleotide polymorphism data for NOV9 is discussed in further detail in Example 3.

Table 9A. NOV9 nucleotide sequence (SEQ ID NO:23).

GCCGCCGCCGCCAAGATGGCGGACCTGGAGGCGGTGCTGGCCGACGTGAGCTACCTGATGGCCATGGAGAAG
AGCAAGGCCACGCCGGCCGCGCGCGCCAGCAAGAAGATACTGCTGCCCGAGCCCAGCATCCGCAGTGTCATG
CAGAAGTACCTGGAGGACCGGGGCGAGGTGACCTTTGAGAAGATCTTTTCCCAGAAGCTGGGGTACCTGCTC
TTCCGAGACTTCTGCCTGAACCACCTGGAGGAGGCCAGGCCCTTGGTGGAATTCTATGAGGAGATCAAGAAG
TACGAGAAGCTGGAGACGGAGGAGGAGCGTGTGGCCCGCAGCCGGGAGATCTTCGACTCATACATCATGAAG
GAGCTGCTGGCCTGCTCGCATCCCTTCTCGAAGAGTGCCACTGAGCATGTCCAAGGCCACCTGGGGAAGAAG
CAGGTGCCTCCGGATCTCTTCCAGCCATACATCGAAGAGATTTGTCAAAACCTCCGAGGGGACGTGTTCCAG
AAATTCATTGAGAGCGATAAGTTCACACGGTTTTGCCAGTGGAAGAATGTGGAGCTCAACATCCACCTGACC
ATGAATGACTTCAGCGTGCATCGCATCATTGGGCGCGGGGGCTTTGGCGAGGTCTATGGGTGCCGGAAGGCT
GACACAGGCAAGATGTACGCCATGAAGTGCCTGGACAAAAAGCGCATCAAGATGAAGCAGGGGGAGACCCTG
GCCCTGAACGAGCGCATCATGCTCTCGCTCGTCAGCACTGGGGACTGCCCATTCATTGTCTGCATGTCATAC
GCGTTCCACACGCCAGACAAGCTCAGCTTCATCCTGGACCTCATGAACGGTGGGGACCTGCACTACCACCTC
TCCCAGCACGGGGTCTTCTCAGAGGCTGACATGCGCTTCTATGCGGCCGAGATCATCCTGGGCCTGGAGCAC
ATGCACAACCGCTTCGTGGTCTACCGGGACCTGAAGCCAGCCAACATCCTTCTGGACGAGCATGGCCACGTG
CGGATCTCGGACCTGGGCCTGGCCTGTGACTTCTCCAAGAAGAAGCCCCATGCCAGCGTGGGCACCCACGGG
TACATGGCTCCGGAGGTCCTGCAGAAGGGCGTGGCCTACGACAGCAGTGCCGACTGGTTCTCTCTGGGGTGC
ATGCTCTTCAAGTTGCTGCGGGGGCACAGCCCCTTCCGGCAGCACAAGACCAAAGACAAGCATGAGATCGAC
CGCATGACGCTGACGATGGCCGTGGAGCTGCCCGACTCCTTCTCCCCTGAACTACGCTCCCTGCTGGAGGGG
TTGCTGCAGAGGGATGTCAACCGGAGATTGGGCTGCCTGGGCCGAGGGGCTCAGGAGGTGAAAGAGAGCCCC
TTTTTCCGCTCCCTGGACTGGCAGATGGTCTTCTTGCAGAAGTACCCTCCCCCGCTGATCCCCCCACGAGGG
GAGGTGAACGCGGCCGACGCCTTCGACATTGGCTCCTTCGATGAGGAGGACACAAAAGGAATCAAGCAGGAG
GTGGCAGAGACTGTCTTCGACACCATCAACGCTGAGACAGACCGGCTGGAGGCTCGCAAGAAAGCCAAGAAC
AAGCAGCTGGGCCATGAGGAAGACTACGCCCTGGGCAAGGACTGCATCATGCATGGCTACATGTCCAAGATG
GGCAACCCCTTCCTGACCCAGTGGCAGCGGCGGTACTTCTACCTGTTCCCCAACCGCCTCGAGTGGCGGGGC
GAGGGCGAGGCCCCGCAGAGCCTGCTGACCATGGAGGAGATCCAGTCGGTGGAGGAGACGCAGATCAAGGAG
CGCAAGTGCCTGCTCCTCAAGATCCGCGGTGGGAAACAGTTCATTTTGCAGTGCGATAGCGACCCTGAGCTG
GTGCAGTGGAAGAAGGAGCTGCGCGACGCCTACCGCGAGGCCCAGCAGCTGGTGCAGCGGGTGCCCAAGATG
AAGAACAAGCCGCGCTCGCCCGTGGTGGAGCTGAGCAAGGTGCCGCTGGTCCAGCGCGGCAGTGCCAACGGC
CTCTGACCCGCCCACCCGCCT

In a search of public sequence databases, the NOV9 nucleic acid sequence, located on chromsome 11 has 1546 of 1574 bases (98%) identical to a beta-adrenergic receptor kinase 1 mRNA from *Homo sapiens*, (GENBANK-ID: HUMBARK1A) (E = 0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV9 polypeptide (SEQ ID NO:24) encoded by SEQ ID NO:23 has 668 amino acid residues and is presented in Table 9B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV9 has no signal peptide and is likely to be localized in the nucleus with a certainty of 0.3000. In other embodiments, NOV9 may also be localized to the microbody (peroxisome) with acertainty of 0.1478, the mitrochondrial matrix (lumen) with a certainty of 0.1000 or in the lysosome (lumen) with a certainty of 0.1000.

Table 9B. Encoded NOV9 protein sequence (SEQ ID NO:24).

MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFSQKLGYLLFRDFC
LNHLEEARPLVEFYEEIKKYEKLETEEERVARSREIFDSYIMKELLACSHPFSKSATEHVQGHLGKKQVPPD

LFQPYIEEICQNLRGDVFQKFIESDKFTRFCQWKNVELNIHLTMNDFSVHRIIGRGGFGEVYGCRKADTGKM
YAMKCLDKKRIKMKQGETLALNERIMLSLVSTGDCPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGV
FSEADMRFYAAEIILGLEHMHNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHASVGTHGYMAPE
VLQKGVAYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPELRSLLEGLLQRD
VNRRLGCLGRGAQEVKESPFFRSLDWQMVFLQKYPPPLIPPRGEVNAADAFDIGSFDEEDTKGIKQEVAETV
FDTINAETDRLEARKKAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLFPNRLEWRGEGEAP
QSLLTMEEIQSVEETQIKERKCLLLKIRGGKQFILQCDSDPELVQWKKELRDAYREAQQLVQRVPKMKNKPR
SPVVELSKVPLVQRGSANGL

A search of sequence databases reveals that the NOV9 amino acid sequence has 495 of 497 amino acid residues (99%) identical to, and 495 of 497 amino acid residues (99%) similar to, the 689 amino acid residue beta-adrenergic receptor kinase from *Homo sapiens* (A53791) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV9 is expressed in at least the following tissues: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

In addition, the sequence is predicted to be expressed in blood leukocytes because of the expression pattern of (GENBANK-ID:gb:GENBANK-ID:HUMBARK1A|acc:M80776.1) a closely related Human beta-adrenergic receptor kinase 1 mRNA, complete cds homolog in species *Homo sapiens*.

The disclosed NOV9 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 9C.

Table 9C. BLAST results for NOV9

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ptnr:pir-id:A53791	beta-adrenergic-receptor kinase (EC 2.7.1.126) 1 - human	689	495/497 (99%)	495/497 (99%)	0.0
ptnr:SWISSPROT-ACC:P25098	Beta-adrenergic receptor kinase 1 (EC 2.7.1.126)	689	494/497 (99%)	495/497 (99%)	0.0
ptnr:SPTREMBL-ACC:Q99LL8	SIMILAR TO ADRENERGIC, BETA, RECEPTOR KINASE 1 - Mus musculus	687	490/495 (98%),	493/495 (99%)	0.0

ptnr:SWISSPROT-ACC:P26817	Beta-adrenergic receptor kinase 1	689	489/497 (98%)	493/497 (99%)	0.0
ptnr:SPTREMBL-ACC:Q99MK8	G PROTEIN RECEPTOR KINASE 2	689	490/497 (98%)	494/497 (99%)	0.0

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 9D. In the ClustalW alignment of the NOV9 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 9D. ClustalW Analysis of NOV9

1) NOV9 (SEQ ID NO:24)
2) ptnr:pir-id:A53791 beta-adrenergic-receptor kinase (EC 2.7.1.126) 1 (SEQ ID NO:69)
3) ptnr:SWISSPROT-ACC:P25098 Beta-adrenergic receptor kinase 1 (EC 2.7.1.126) (SEQ ID NO:70)
4) ptnr:SPTREMBL-ACC:Q99LL8 SIMILAR TO ADRENERGIC, BETA, RECEPTOR KINASE 1 - Mus musculus (Mouse) (SEQ ID NO:71)
5) 6) ptnr:SWISSPROT-ACC:P26817 Beta-adrenergic receptor kinase 1 (EC 2.7.1.126) (Beta-ARK-1) (SEQ ID NO:72)

```
NOV9     MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
A53791   MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
P25098   MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
Q99LL8   --DLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 58
P26817   MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60

NOV9     QKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSREIFDSYIMKELLAC 120
A53791   QKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSREIFDSYIMKELLAC 120
P25098   QKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSREIFDSYIMKELLAC 120
Q99LL8   QKLGYLLFRDFCLNHLEEAKPLVEFYEEIKKYEKLETEEERVVRSREIFDSYIMKELLAC 118
P26817   QKLGYLLFRDFYLNHLEEAKPLVEFYEEIEKYEKLETEEERVVRSREIFDSYIMKELLAC 120

NOV9     SHPFSKSATEHVQGHLGKKQVPPDLFQPYIEEICQNLRGDVFQKFIESDKFTRFCQWKNV 180
A53791   SHPFSKSATEHVQGHLGKKQVPPDLFQPYIEEICQNLRGDVFQKFIESDKFTRFCQWKNV 180
P25098   SHPFSKSATEHVQGHLGKKQVPPDLFQPYIEEICQNLRGDVFQKFIESDKFTRFCQWKNV 180
Q99LL8   SHPFSKNATEHVQGHLVKKQVPPDLFQPYIEEICQNLRGDVFQKFIESDKFTRFCQWKNV 178
P26817   SHPFSKNATEHVQGHLVKKQVPPDLFQPYIEEICQNLRGDVFHKFIESDKFTRFCQWKNV 180

NOV9     ELNIHLTMNDFSVHRIIGRGGFGEVYGCRKADTGKMYAMKCLDKKRIKMKQGETLALNER 240
A53791   ELNIHLTMNDFSVHRIIGRGGFGEVYGCRKRDTGKMYAMKCLDKKRIKMKQGETLALNER 240
P25098   ELNIHLTMNDFSVHRIIGRGGFGEVYGCRKRDTGKMYAMKCLDKKRIKMKQGETLALNER 240
Q99LL8   ELNIHLTMNDFSVHRIIGRGGFGEVYGCRKADTGKMYAMKCLDKKRIKMKQGETLALNER 238
P26817   ELNIHLTMNDFSVHRIIGRGGFGEVYGCRKADTGKMYAMKCLDKKRIKMKQGETLALNER 240

NOV9     IMLSLVSTGDCPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE 300
A53791   IMLSLVSTGDCPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE 300
P25098   IMLSLVSTGDCPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE 300
Q99LL8   IMLSLVSTGDCPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE 298
P26817   IMLSLVSTGDCPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE 300

NOV9     IILGLEHMHNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHASVGTHGYMAPE 360
A53791   IILGLEHMHNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHASVGTHGYMAPE 360
```

```
P25098  IILGLEHMHNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHASVGTHGYMAPE 360
Q99LL8  IILGLEHMHNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKRPHASVGTHGYMAPE 358
P26817  IILGLEHMHNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHASVGTHGYMAPE 360

NOV9    VLQKGVAYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE 420
A53791  VLQKGVAYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE 420
P25098  VLQKGVAYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE 420
Q99LL8  VLQKGVAYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE 418
P26817  VLQKGVAYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE 420

NOV9    LRSLLEGLLQRDVNRRLGCLGRGAQEVKESPFFRSLDWQMVFLQKYPPPLIPPRGEVNAA 480
A53791  LHSLLEGLLQRDVNRRLGCLGRGAQEVKESPFFRSLDWQMVFLQKYPPPLIPPRGEVNAA 480
P25098  LHSLLEGLLQRDVNRRLGCLGRGAQEVKESPFFRSLDWQMVFLQRYPPPLIPPRGEVNAA 480
Q99LL8  LRSLLEGLLQRDVNRRLGCLGRGAQEVKESPFFRSLDWQMVFLQKYPPPLIPPRGEVNAA 478
P26817  LRSLLEGLLQRDVNRRLGCLGRGAQEIKESPFFRSLDWQMVFLQKYPPPLIPPRGEVNAA 480

NOV9    DAFDIGSFDEEDTKGIK--------------------QEVAETVFDTINAETDRLEARK 519
A53791  DAFDIGSFDEEDTKGIKLLDSDQELYRNFPLTISERWQQEVAETVFDTINAETDRLEARK 540
P25098  DAFDIGSFDEEDTKGIKLLDSDQELYRNFPLTISERWQQEVAETVFDTINAETDRLEARK 540
Q99LL8  DAFDIGSFDEEDTKGIKLLDSDQELYRNFPLTISERWQQEVAETVFDTINAETDRLEARK 538
P26817  DAFDIGSFDEEDTKGIKLLDSDQELYRNFPLTISERWQQEVAETVFDTINAETDRLEARK 540

NOV9    KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLFPNRLEWRGEGEAPQSL 579
A53791  KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLFPNRLEWRGEGEAPQSL 600
P25098  KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLFPNRLEWRGEGEAPQSL 600
Q99LL8  KAKNKQLGHEEDYALGKDCIVHGYMSKMGNPFLTQWQRRYFYLFPNRLEWRGEGEAPQSL 598
P26817  KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLFPNRLEWRGEDEAPQSL 600

NOV9    LTMEEIQSVEETQIKERKCLLLKIRGGKQFILQCDSDPELVQWKKELRDAYREAQQLVQR 639
A53791  LTMEEIQSVEETQIKERKCLLLKIRGGKQFILQCDSDPELVQWKKELRDAYREAQQLVQR 660
P25098  LTMEEIQSVEETQIKERKCLLLKIRGGKQFILQCDSDPELVQWKKELRDAYREAQQLVQR 660
Q99LL8  LTMEEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR 658
P26817  LTMEEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR 660

NOV9    VPKMKNKPRSPVVELSKVPLVQRGSANGL 668
A53791  VPKMKNKPRSPVVELSKVPLVQRGSANGL 689
P25098  VPKMKNKPRSPVVELSKVPLVQRGSANGL 689
Q99LL8  VPKMKNKPRSPVVELSKVPLIQRGSANGL 687
P26817  VPKMKNKPRSPVVELSKVPLIQRGSANGL 689
```

Tables 9E-9L list the domain descriptions from DOMAIN analysis results against NOV9. This indicates that the NOV9 sequence has properties similar to those of other proteins known to contain this domain.

Table 9E. Domain Analysis of NOV9

gnl|Smart|smart00220, S_TKc, Serine/Threonine protein kinases, catalytic domain; Phosphotransferases. Serine or threonine-specific kinase subfamily. (SEQ ID NO:98)
CD-Length = 256 residues, 100.0% aligned
Score = 237 bits (604), Expect = 2e-63

```
Query:  191  FSVHRIIGRGGFGEVYGCRKADTGKMYAMKCLDKKRIKMKQGETLALNERIMLSLVSTGD  250
Sbjct:  1    YELLEVLGKGAFGKVYLARDKKTGKLVAIKVIKKEKLKKKKRER-ILREIKILKKL---D  56

Query:  251  CPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAEIILGLEHMHN  310
Sbjct:  57   HPNIVKLYDVFEDDDKLYLVMEYCEGGDLFDLLKKRGRLSEDEARFYARQILSALEYLHS  116

Query:  311  RFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHAS--VGTHGYMAPEVLQKGVAY  368
```

```
Sbjct:  117  QGIIHRDLKPENILLDSDGHVKLADFGLAKQLDSGGTLLTTFVGTPEYMAPEVL-LGKGY  175

Query:  369  DSSADWFSLGCMLFKLLRGHSPFRQHKTKDK-HEIDRMTLTMAVELPDSFSPELRSLLEG  427
               + | +||| +|++|| |  ||          +                ||| + |++
Sbjct:  176  GKAVDIWSLGVILYELLTGKPPFPGDDQLLALFKKIGKPPPPFPPPEWKISPEAKDLIKK  235

Query:  428  LLQRDVNRRLGCLGRGAQEVKESPFF  453
             || +|  +||      |+|  | |||
Sbjct:  236  LLVKDPEKRL-----TAEEALEHPFF  256
```

Table 9F. Domain Analysis of NOV9

gnl|Pfam|pfam00069, pkinase, Protein kinase domain. (SEQ ID NO:99)
CD-Length = 256 residues, 100.0% aligned
Score = 221 bits (562), Expect = 1e-58

```
Query:  191  FSVHRIIGRGGFGEVYGCRKADTGKMYAMKCLDKKRIKMKQGETLALNERIMLSLVSTGD  250
             + +   +| | ||+||  +  |||++ |+| | |+ +  |+   |   | +|  +|
Sbjct:  1    YELGEKLGSGAFGKVYKGKHKDTGEIVAIKILKKRSLSEKKKRFL--REIQILRRLS---  55

Query:  251  CPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVF-SEADMRFYAAEIILGLEHMH  309
              | || +   |   | |  +++ | ||||  +| ++|+  || + +  | +|+ |||++|
Sbjct:  56   HPNIVRLLGVFEEDDHLYLVMEYMEGGDLFDYLRRNGLLLSEKEAKKIALQILRGLEYLH  115

Query:  310  NRFVVYRDLKPANILLDEHGHVRISDLGLACDF---SKKKPHASVGTHGYMAPEVLQKGV  366
             +| +|+|||||  ||||||+| |+|+| |||      | +|    |||  |||||||  +|
Sbjct:  116  SRGIVHRDLKPENILLDENGTVKIADFGLARKLESSSYEKLTTFVGTPEYMAPEVL-EGR  174

Query:  367  AYDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPELRSLLE  426
              | |  | +||| +|++|| |  ||      ++    +    + + || + | ||+ |++
Sbjct:  175  GYSSKVDVWSLGVILYELLTGKLPFPGIDPLEELFRIKERPRLRLPLPPNCSEELKDLIK  234

Query:  427  GLLQRDVNRRLGCLGRGAQEVKESPFF  453
               | +|  +|       |+|+   |+|
Sbjct:  235  KCLNKDPEKRP-----TAKEILNHPWF  256
```

Table 9G. Domain Analysis of NOV9

gnl|Pfam|pfam00615, RGS, Regulator of G protein signaling domain. RGS family members are GTPase-activating proteins for heterotrimeric G-protein alpha-subunits. (SEQ ID NO:106)
CD-Length = 119 residues, 100.0% aligned
Score = 130 bits (326), Expect = 3e-31

```
Query:  54   TFEKIFSQKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSREIFDSYI  113
             +|||+  | +|  ||||+|      |    +||+  +++|||  |  ++|  ++|||+| +|
Sbjct:  1    SFEKLLKQPIGRLLFREFLETEFSE--ENLEFWLAVEEYEKTEDPDKRPDKAREIYDEFI  58

Query:  114  MKELLACSHPFSKSATEHVQGHLGKKQVPPDLFQPYIEEICQNLRGDVFQKFIESDKFTR  173
               |              || | +|  |    |||+    ||   +||| | +|+|||| |||
Sbjct:  59   SPEAPKPEVNLDSELREHTQDNL-LKAPTKDLFEEAQREIYDLMRGDSFPRFLESDYFTR  117

Query:  174  FC  175
             |
Sbjct:  118  FL  119
```

Table 9H. Domain Analysis of NOV9

gnl|Smart|smart00219, TyrKc, Tyrosine kinase, catalytic domain; Phosphotransferases. Tyrosine-specific kinase subfamily. (SEQ ID NO:100)
CD-Length = 258 residues, 94.6% aligned
Score = 110 bits (275), Expect = 3e-25

```
Query:  195  RIIGRGGFGEVYGCR---KADTGKMYAMKCLDKKRIKMKQGETLALNE-RIMLSLVSTGD  250
Sbjct:  5    KKLGEGAFGEVYKGTLKGKGGVEVEVAVKTL--KEDASEQQIEEFLREARLMRKL----D  58

Query:  251  CPFIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHG--VFSEADMRFYAAEIILGLEHM  308
Sbjct:  59   HPNIVKLLGVCTEEEPLMIVMEYMEGGDLLDYLRKNRPKELSLSDLLSFALQIARGMEYL  118

Query:  309  HNRFVVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHASVGTHG----YMAPEVLQK  364
Sbjct:  119  ESKNFVHRDLAARNCLVGENKTVKIADFGLARDLYDDDYYRKKKSPRLPIRWMAPESLKD  178

Query:  365  GVAYDSSADWFSLGCMLFKLL-RGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPELRS  423
Sbjct:  179  GK-FTSKSDVWSFGVLLWEIFTLGESPY--PGMSNEEVLEYLKKGYRLPQPPNCPDEIYD  235

Query:  424  LLEGLLQRDVNRR  436
Sbjct:  236  LMLQCWAEDPEDR  248
```

Table 9I. Domain Analysis of NOV9

gnl|Smart|smart00315, RGS, Regulator of G protein signalling domain; RGS family members are GTPase-activating proteins for heterotrimeric G-protein alpha-subunits. (SEQ ID NO:107)
CD-Length = 119 residues, 100.0% aligned
Score = 100 bits (248), Expect = 3e-22

```
Query:  54   TFEKIFSQKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSREIFDSYI  113
Sbjct:  1    SLESLLRDPIGRLLFREFLESEFSE--ENLEFWLAVEEFKKAEDEEERRSKAKEIYDKYL  58

Query:  114  MKELLACSHPFSKSATEHVQGHLGKKQVPPDLFQPYIEEICQNLRGDVFQKFIESDKFTR  173
Sbjct:  59   SPNAPKE-VNLDSDLREEIEENLKNEEPPPDLFDEAQEEVYELLEKDSYPRFLESDYYLR  117

Query:  174  FC  175
Sbjct:  118  FL  119
```

Table 9J. Domain Analysis of NOV9

gnl|Smart|smart00233, PH, Pleckstrin homology domain.; Domain commonly found in eukaryotic signalling proteins. The domain family possesses multiple functions including the abilities to bind inositol phosphates, and various proteins. PH domains have been found to possess inserted domains (such as in PLC gamma, syntrophins) and to be inserted within other domains. Mutations in Brutons tyrosine kinase (Btk) within its PH domain cause X-linked agammaglobulinaemia (XLA) in patients. Point mutations cluster into the positively charged end of the molecule around the predicted binding site for phosphatidylinositol lipids. (SEQ ID NO:108)
CD-Length = 104 residues, 95.2% aligned
Score = 62.0 bits (149), Expect = 1e-10

```
Query:  539  IMHGYMSKMGNPFLTQWQRRYFYLFPNRLEW-----RGEGEAPQSLLTMEEIQ---SVEE  590
             |  |++ |  +      |++|||  ||    | +      +      |+  + +        + +
Sbjct:  2    IKEGWLLKKSSGGKKSWKKRYFVLFNGVLLYYKSKKKKSSSKPKGSIPLSGCTVREAPDS  61

Query:  591  TQIKERKCLLLKIRGGKQFILQCDSDPELVQWKKELRDA  629
                |++ |  +      |  +|| +|+ |  +| + || |
Sbjct:  62   DSDKKKNCFEIVTPDRKTLLLQAESEEERKEWVEALRKA  100
```

Table 9K. Domain Analysis of NOV9

gnl|Pfam|pfam00169, PH, PH domain. PH stands for pleckstrin homology. (SEQ ID NO:109)
CD-Length = 100 residues, 97.0% aligned
Score = 55.5 bits (132), Expect = 1e-08

```
Query:  539  IMHGYMSKMGNPFLTQWQRRYFYLFPNRLEW---RGEGEAPQSLLTMEEIQSVEETQIKE  595
             +  |++ |        +|++|||+|| + | +   + +   |+  + +      +    +
Sbjct:  2    VKEGWLLKKSTVKKKRWKKRYFFLFNDVLIYYKDKKKSYEPKGSIPLSGCSVEDVPDSEF  61

Query:  596  RKCLLLKIR---GGKQFILQCDSDPELVQWKKELRDA  629
             ++    ++|    | + |||| +|+ |    | | ++ |
Sbjct:  62   KRPNCFQLRSRDGKETFILQAESEEERQDWIKAIQSA  98
```

Table 9L. Domain Analysis of NOV9

gnl|Smart|smart00133, S_TK_X, Extension to Ser/Thr-type protein kinases (SEQ ID NO:110)
CD-Length = 63 residues, 87.3% aligned
Score = 42.7 bits (99), Expect = 7e-05

```
Query:  454  RSLDWQMVFLQKYPPPLIPPRGEVNAADAFDIGSFDEEDTKGIKQEVAETVFDTINAETD  513
             | +||  +  ++  || +|           |  +|| | |   ++    |  |   +|+|
Sbjct:  1    RGIDWDKLENKEIEPPFVPKVK-----SPTDTSNFDPEFT---EESPVLTPVDPPLSESD  52

Query:  514  RLE  516
             + |
Sbjct:  53   QDE  55
```

Eukaryotic protein kinases are enzymes that belong to a very extensive family of proteins which share a conserved catalytic core common with both serine/threonine and tyrosine protein kinases. There are a number of conserved regions in the catalytic domain of protein kinases. In the N-terminal extremity of the catalytic domain there is a glycine-rich stretch of residues in the vicinity of a lysine residue, which has been shown to be involved in ATP binding. In the central part of the catalytic domain there is a conserved aspartic acid residue which is important for the catalytic activity of the enzyme.

The beta-adrenergic receptor kinase (beta ARK) catalyses the phosphorylation of the activated forms of the beta 2-adrenergic receptor (beta 2AR). The interaction between receptor and kinase is independent of second messengers and appears to involve a multipoint attachment of kinase and substrate with the specificity being restricted by both the primary amino acid sequence and conformation of the substrate. Kinetic, functional and sequence information reveals that rhodopsin kinase and beta ARK are closely related, suggesting they are members of a family of G-protein-coupled receptor kinases.

The beta-adrenergic signaling cascade is an important regulator of myocardial function. Significant alterations of this pathway are associated with several cardiovascular diseases, including congestive heart failure (CHF). CHF patients share several similar features, such as reduced cardiac contractility and neurohumoral activation to compensate the impaired cardiac function. In CHF patients, the cardiac renin-angitensin (RA) system, receptors, GTP-binding proteins, and their effector molecules are inevitably exposed to chronically elevated neurohumoral stimulation. A widely recognized concept is that a chronic increase in such stimulation can desensitize target cell receptors and the post-receptor signal transducing pathway. Included in these alterations is increased activity and expression of G protein-coupled receptor kinases (GRKs), such as the beta-adrenergic receptor kinase (beta ARK1), which phosphorylate and desensitize beta-adrenergic receptors (beta ARs). A body of evidence is accumulating that suggests that GRKs, in particular beta ARK1, are critical determinants of cardiac function under normal conditions and in disease states. Transgenic mice with myocardial-targeted alterations of GRK activity have shown profound changes in the in vivo functional performance of the heart. Included in these studies is the compelling finding that inhibition of beta ARK1 activity or expression significantly enhances cardiac function and potentiates beta AR signaling in failing cardiomyocytes. An uncoupling of beta2-adrenoceptors has been attributed to an increased activity and gene expression of beta-adrenergic receptor kinase in failing myocardium, leading to phosphorylation and uncoupling

of receptors. The important physiological function of GRK2 as a modulator of the efficacy of GPCR signal transduction systems is exemplified by its relevance in cardiovascular physiopathology as well as by its emerging role in the regulation of chemokine receptors.

The disclosed NOV9 nucleic acid of the invention encoding a Beta-adrenergic receptor kinase-like protein includes the nucleic acid whose sequence is provided in Table 9A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 9A while still encoding a protein that maintains its Beta-adrenergic receptor kinase-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 2 percent of the bases may be so changed.

The disclosed NOV9 protein of the invention includes the Beta-adrenergic receptor kinase-like protein whose sequence is provided in Table 9B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 9B while still encoding a protein that maintains its Beta-adrenergic receptor kinase-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 1 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the beta-adrenergic receptor kinase-like protein and the NOV9 proteins disclosed herein suggest that this beta-adrenergic receptor kinase may have important structural and/or physiological functions characteristic of the Ser/Thr protein kinases family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene

delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

The NOV9 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from heart failure, hypertension, secondary pathologies caused by heart failure and hypertension, and other diseases, disorders and conditions of the like. Additionally, the compositions of the present invention may have efficacy for treatment of patients suffering from conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors.. The NOV9 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV9 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV9 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV9 epitope is from about amino acids 40 to 70. In another embodiment, the comtemplated NOV9 epitope is from about amino acids 80 to 110. In further embodiments, the contemplated NOV9 epitope is from about amino acids 120 to 200, from about amino acids 220 to 245, from about amino acids 250 to 280, or from about amino acids 290 to 340. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV10

A disclosed NOV10 nucleic acid of 3003 nucleotides (also referred to as AC058790_da25) encoding an alpha-mannosidase-like protein is shown in Table 10A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 57-59 and ending with a TAA codon at nucleotides 2946-2948. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 10A. The start and stop codons are in bold letters. Single nucleotide polymorphism data is included in Example 3.

Table 10A. NOV10 nucleotide sequence (SEQ ID NO:25).

GGTATCATACTCCAGCAAGCGCACATCATCAGTGACGTCGATCACGATGCATCGTCATGGCGGCAGCGCCGTTCTTGAAG
CACTGGCGCACCACTTTTGAGCGGGTGGAGAAGTTCGTGTCCCCGATCTACTTCACCGACTGTAACCTCCGCGGCAGGCT
TTTTGGGGCCAGCTGCCCTGTGGCTGTGCTCTCCAGCTTCCTGACGCCGGAGAGACTTCCCTACCAGGAGGCAGTCCAGC
GGGACTTCCGCCCCGCGCAGGTCGGCGACAGCTTCGGACCCACATGGTGGACCTGCTGGTTCCGGGTGGAGCTGACCATC
CCAGAGGCATGGGTGGGCCAGGAAGTTCACCTTTGCTGGGAAAGTGATGGAGAAGGTCTGGTGTGGCGTGATGGAGAACC
TGTCCAGGGTTTAACCAAAGAGGGTGAGAAGACCAGCTATGTCCTGACTGACAGGCTGGGGGAAAGAGACCCCCGAAGCC
TCACTCTCTATGTGGAAGTAGCCTGCAATGGGCTCCTGGGGGCCGGGAAGGGAAGCATGATTGCAGCCCCTGACCCTGAG
AAGATGTTCCAGCTGAGCCGGGCTGAGCTAGCTGTGTTCCACCGGGATGTCCACATGCTCCTGGTGGATCTGGAGCTGCT
GCTGGGCATAGCCAAGGCGCAGCAGCTGGAATGGGTGAAGAGCCGCTACCCTGGCCTGTACTCCCGCATCCAGGAGTTTG
CGTGCCGTGGGCAGTTTGTGCCTGTGGGGGGCACCTGGGTGGAGATGGATGGGAACCTGCCCAGTGGAGAGGCCATGGTG
AGGCAGTTTTTGCAGGGCCAGAACTTCTTTCTGCAGGAGTTTGGGAAGATGTGCTCTGAGTTCTGGCTGCCGGACACCTT
TGGCTACTCAGCACAGCTCCCCCAGATCATGCACGGCTGTGGCATCAGGCGCTTTCTCACCCAGAAATTGAGCTGGAATT
TGGTGAACTCCTTCCCACACCATACATTTTTCTGGGAGGGCCTGGATGGCTCCCGTGTACTGGTCCACTTCCCACCTGGC
GACTCCTATGGGATGCAGGGCAGCGTGGAGGAGGTGCTGAAGACCGTGGCCAACAACCGGGACAAGGGGCGGGCCAACCA
CAGTGCCTTCCTCTTTGGCTTTGGGGATGGGGGTGGTGGCCCCACCCAGACCATGCTGGACCGCCTGAAGCGCCTGAGCA
ATACGGATGGGCTGCCCAGGGTGCAGCTATCTTCTCCAAGACAGCTCTTCTCAGCACTGGAGAGTGACTCAGAGCAGCTG
TGCACGTGGGTTGGGGAGCTCTTCTTGGAGCTGCACAATGGCACATACACCACCCATGCCCAGATCAAGAAGGGGAACCG
GGAATGTGAGCGGATCCTGCACGACGTGGAGCTGCTCAGTAGCCTGGCCCTGGCCCGCAGTGCCCAGTTCCTATACCCAG
CAGCCCAGCTGCAGCACCTCTGGAGGCTCCTTCTTCTGAACCAGTTCCATGATGTGGTGACTGGAAGCTGCATCCAGATG
GTGGCAGAGGAAGCCATGTGCCATTATGAAGACATCCGTTCCCATGGCAATACACTGCTCAGCGCTGCAGCCGCAGCCCT
GTGTGCTGGGGAGCCAGGTCCTGAGGGCCTCCTCATCGTCAACACACTGCCCTGGAAGCGGATCGAAGTGATGGCCCTGC
CCAAACCGGGCGGGGCCCACAGCCTAGCCCTGGTGACAGTGCCCAGCATGGGCTATGCTCCTGTTCCTCCCCCCACCTCA
CTGCAGCCCCTGCTGCCCCAGCAGCCTGTGTTCGTAGTGCAAGAGACTGATGGCTCCGTGACTCTGGACAATGGCATCAT
CCGAGTGAAGCTGGACCCAACTGGTCGCCTGACGTCCTTGGTCCTGGTGGCCTCTGGCAGGGAGGCCATTGCTGAGGGCG
CCGTGGGGAACCAGTTTGTGCTATTTGATGATGTCCCCTTGTACTGGGATGCATGGGACGTCATGGACTACCACCTGGAG
ACACGGAAGCCTGTGCTGGGCCAGGCAGGGACCCTGGCAGTGGGCACCGAGGGCGGCCTGCGGGGCAGCGCCTGGTTCTT
GCTACAGATCAGCCCCAACAGTCGGCTTAGCCAGGAGGTTGTGCTGGACGTTGGCTGCCCCTATGTCCGCTTCCACACCG
AGGTACACTGGCATGAGGCCCACAAGTTCCTGAAGGTGGAGTTCCCTGCTCGCGTGCGGAGTTCCCAGGCCACCTATGAG
ATCCAGTTTGGGCACCTGCAGCGACCTACCCACTACAATACCTCTTGGGACTGGGCTCGATTTGAGGTGTGGGCCCATCG
CTGGATGGATCTGTCAGAACACGGCTTTGGGCTGGCCCTGCTCAACGACTGCAAGTATGGCGCGTCAGTGCGAGGCAGCA
TCCTCAGCCTCTCGCTCTTGCGGGCGCCTAAAGCCCCGGACGCTACTGCTGACACGGGGCGCCACGAGTTCACCTATGCA
CTGATGCCGCACAAGGGCTCTTTCCAGGATGCTGGCGTTATCCAAGCTGCCTACAGCCTAAACTTCCCCCTGTTGGCTCT
GCCAGCCCCCAGCCCAGCGCCCGCCACCTCCTGGAGTGCGTTTTCCGTGTCTTCACCCGCGGTCGTATTGGAGACCGTCA
AGCAGGCGGAGAGCAGCCCCCAGCGCCGCTCGCTGGTCCTGAGGCTGTATGAGGCCCACGGCAGCCACGTGGACTGCTGG
CTGCACTTGTCGCTGCCGGTTCAGGAGGCCATCCTCTGCGATCTCTTGGAGCGACCAGACCCTGCTGGCCACTTGACTTC
GGGACAACCGCCTGAAGCTCACCTTTTCTCCCTTCCAAGTGCTGTCCCTGTTGCTCGTGCTTCAGCCTCCGCCACACTGA
GTCCCTGGGGCTGGGGTTTTGTTTGTAGAAGGCTCTGGGGACTCCTAATTTCTGCTTCCCCAGCCTAAAGCAGGGATCAG
TCTTTTCTTGTGGAATAAATCCTTGGATCGGGAAAAAAAAAAA

In a search of public sequence databases, the NOV10 nucleic acid sequence, located on chromsome 15 has 2371 of 2390 bases (99%) identical to a alpha-mannosidase mRNA from *Homo sapiens*, (GENBANK-ID: AF044414| acc: AF044414.2) (E = 0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV10 polypeptide (SEQ ID NO:26) encoded by SEQ ID NO:25 has 963 amino acid residues and is presented in Table 10B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV10 does not have a signal peptide and is likely to be localized in the peroxisome (microbody) with a certainty of 0.7480. In other embodiments, NOV10 is also likely to be localized to the mitochondrial membrane space with a certainty of 0.4539, to the mitochondrial intermembrane space with a certainty of 0.4027, or to the lysosome (lumen) with a certainty of 0.2317.

Table 10B. Encoded NOV10 protein sequence (SEQ ID NO:26).

```
MAAAPFLKHWRTTFERVEKFVSPIYFTDCNLRGRLFGASCPVAVLSSFLTPERLPYQEAVQRDFRPAQVGDS
FGPTWWTCWFRVELTIPEAWVGQEVHLCWESDGEGLVWRDGEPVQGLTKEGEKTSYVLTDRLGERDPRSLTL
YVEVACNGLLGAGKGSMIAAPDPEKMFQLSRAELAVFHRDVHMLLVDLELLLGIAKAQQLEWVKSRYPGLYS
RIQEFACRGQFVPVGGTWVEMDGNLPSGEAMVRQFLQGQNFFLQEFGKMCSEFWLPDTFGYSAQLPQIMHGC
GIRRFLTQKLSWNLVNSFPHHTFFWEGLDGSRVLVHFPPGDSYGMQGSVEEVLKTVANNRDKGRANHSAFLF
GFGDGGGGPTQTMLDRLKRLSNTDGLPRVQLSSPRQLFSALESDSEQLCTWVGELFLELHNGTYTTHAQIKK
GNRECERILHDVELLSSLALARSAQFLYPAAQLQHLWRLLLLNQFHDVVTGSCIQMVAEEAMCHYEDIRSHG
NTLLSAAAAALCAGEPGPEGLLIVNTLPWKRIEVMALPKPGGAHSLALVTVPSMGYAPVPPPTSLQPLLPQQ
PVFVVQETDGSVTLDNGIIRVKLDPTGRLTSLVLVASGREAIAEGAVGNQFVLFDDVPLYWDAWDVMDYHLE
TRKPVLGQAGTLAVGTEGGLRGSAWFLLQISPNSRLSQEVVLDVGCPYVRFHTEVHWHEAHKFLKVEFPARV
RSSQATYEIQFGHLQRPTHYNTSWDWARFEVWAHRWMDLSEHGFGLALLNDCKYGASVRGSILSLSLLRAPK
APDATADTGRHEFTYALMPHKGSFQDAGVIQAAYSLNFPLLALPAPSPAPATSWSAFSVSSPAVVLETVKQA
ESSPQRRSLVLRLYEAHGSHVDCWLHLSLPVQEAILCDLLERPDPAGHLTSGQPPEAHLFSLPSAVPVARAS
ASATLSPWGWGFVCRRLWGLLISASPA
```

A search of sequence databases reveals that the NOV10 amino acid sequence has 764of 771 amino acid residues (99%) identical to, and 767 of 771 amino acid residues (99%) similar to, the 1062 amino acid residue alpha-mannosidase protein from *Homo sapiens* (Q9UL64) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV10 was derived from a pool of the following tissues: Adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus, Bone, Cervix, Chorionic Villus, Colon, Liver, Lung, Lymph node, Lymphoid tissue, Ovary, Peripheral Blood, Skin, Stomach, Tonsils, Whole Organism. Thus, it is expressed in at least some of the above tissues. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Genomic Clone sources, Literature sources, and/or RACE sources.

The disclosed NOV10 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 10C.

Table 10C. BLAST results for NOV10

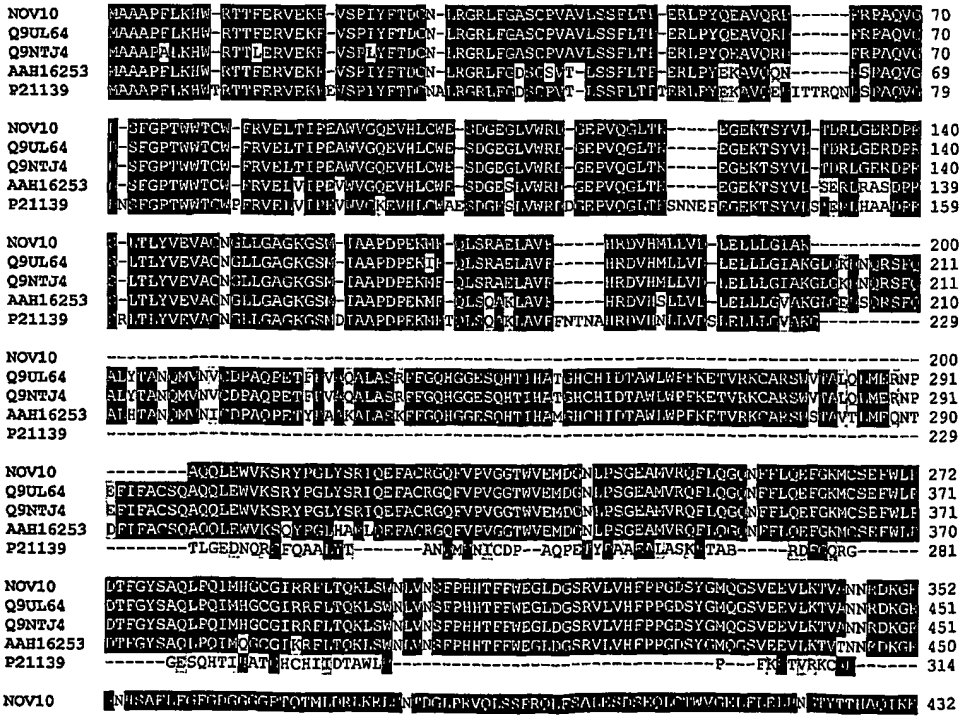
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ptnr:SPTREMBL-ACC:Q9UL64	ALPHA MANNOSIDASE 6A8B - Homo sapiens	1062	763/771 (99%)	767/771 (99%)	0.0

ptnr:SPTREMBL-ACC:Q9NTJ4	HYPOTHETICAL 115.8 KDA PROTEIN - Homo sapiens	1040	715/722 (99%)	718/722 (99%)	0.0
ptnr:TREMBLNEW-ACC:AAH16253	SIMILAR TO MANNOSIDASE, ALPHA, CLASS 2C, MEMBER 1	1039	635/730 (89%),	692/730 (94%)	0.0
ptnr:SWISSPROT-ACC:P21139	Alpha-mannosidase (EC 3.2.1.24)	1040	625/731 (85%)	661/731 (90%)	0.0
ptnr:SPTREMBL-ACC:Q13358	ALPHA-MANNOSIDASE - Homo sapiens	425	425/425 (100%)	425/425 (100%)	0.0

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 10D. In the ClustalW alignment of the NOV10 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 10D. ClustalW Analysis of NOV10

1) NOV10 (SEQ ID NO:26)
2) ptnr: ALPHA MANNOSIDASE 6A8B - Homo sapiens (SEQ ID NO:73)
3) ptnr: HYPOTHETICAL 115.8 KDA PROTEIN - Homo sapiens (SEQ ID NO:74)
4) ptnr: SIMILAR TO MANNOSIDASE, ALPHA, CLASS 2C, MEMBER 1 (SEQ ID NO:75)
5) ptnr: Alpha-mannosidase (EC 3.2.1.24) (SEQ ID NO:76)



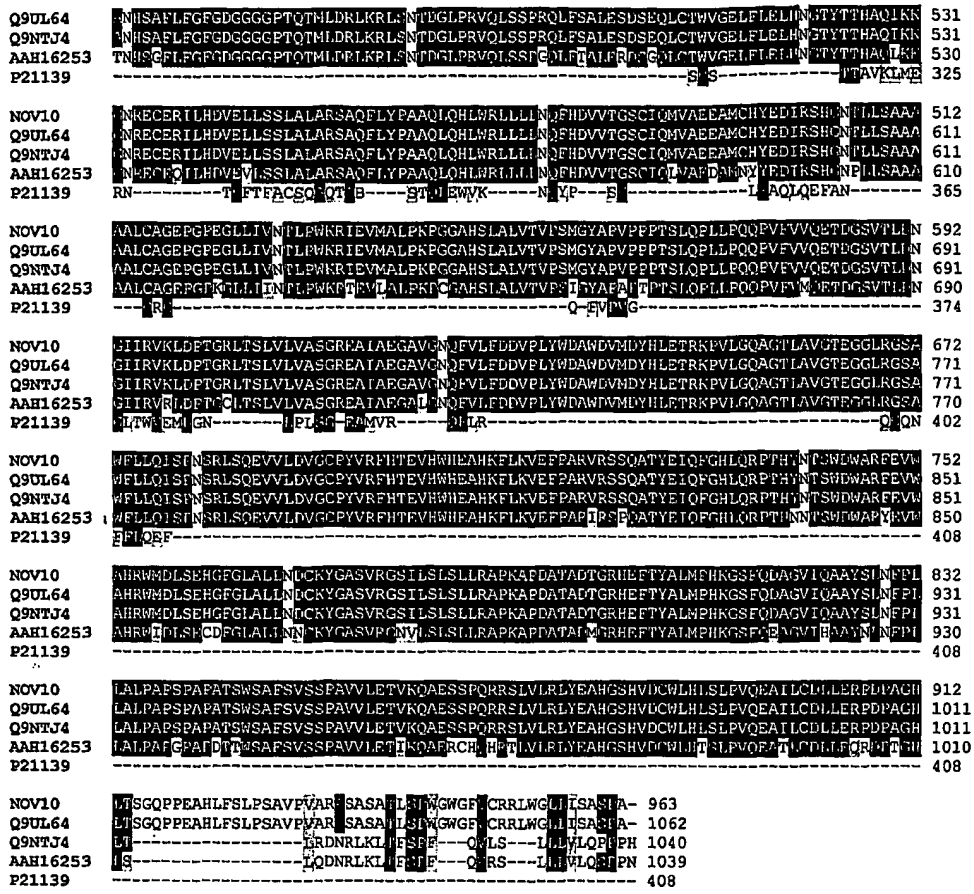


Table 10E lists the domain description from DOMAIN analysis results against NOV10. This indicates that the NOV10 sequence has properties similar to those of other proteins known to contain this domain.

Table 10E. Domain Analysis of NOV10

Model	Description	Score	E-value
Glyco_hydro_38 (InterPro) (SEQ ID NO:111)	Glycosyl hydrolases family 38	140.5	1e-39

```
Glyco_hydro_38: domain 1 of 2, from 230 to 332: score 89.2, E = 5.4e-25
                  *->vtGGWVMnDEAttHyedlIdQlteGHqfLeenfGsdvkPkvgWsIDP
                     |+|+||+ | + +++|++++|++ |+ |+ ++||   +   +|++|+
  AC058790_d   230    VGGTWVEMDGNLPSGEAMVRQFLQGQNFFLQEFG--KMCSEFWLPDT 274

                    FGHSatmPyLlraqaGfdgflIqRihYadKksfaetkqleFvWRqswslt
                    ||+||++|++   +   |+ +||+|++++++ +||++++    |+|      |+
  AC058790_d   275 FGYSAQLPQIM-HGCGIRRFLTQKLSWNLVNSFPHHT---FFWE---GLD 317


                    gstdlfthmmpfysYd<-*
                    ||  +++| +| +||+
  AC058790_d   318 GS-RVLVHFPPGDSYG     332

Glyco_hydro_38: domain 2 of 2, from 410 to 490: score 49.2, E = 1.7e-13
                  *->pYAdepdeGkPeYWTGYFTSRPalKrldRqlehlLrsaEilatqlsv
                     ++ +|++     | + |++|++++ |+ +|++|   |+++|+|++++ +
  AC058790_d   410    TWVGELFL---ELHNGTYTTHAQIKKGNRECERILHDVELLSSLALA 453
```

```
                  lagqskiegsyAiKleklyeqleelRralaLfQHHDAiTGTakqhVv<-*
                      +++++     +     ||+ |+|  |+|+|+||++||+++|+|+
AC058790_d    454 RS-AQFLYPA-----A-----QLQHLWRLLLLNQFHDVVTGSCIQMVA    490
```

Glycosyl hydrolases are key enzymes of carbohydrate metabolism. Lysosomal alpha-mannosidase is necessary for the catabolism of N-linked carbohydrates released during glycoprotein turnover. The enzyme catalyzes the hydrolysis of terminal, non-reducing alpha-D-mannose residues in alpha-D-mannosides, and can cleave all known types of alpha-mannosidic linkages. While alpha-mannosidases were classified as enzymes that process newly formed N-glycans or degrade mature glycoproteins, two endoplasmic reticulum (ER) alpha-mannosidases with previously assigned processing roles, have important catabolic activities. The ER/cytosolic mannosidase may be involved in the degradation of dolichol intermediates that are not needed for protein glycosylation, whereas the soluble form of Man9-mannosidase is responsible for the degradation of glycans on defective or malfolded proteins that are specifically retained and broken down in the ER. The degradation of oligosaccharides derived from dolichol intermediates by ER/cytosolic mannosidase explains why cats and cattle with alpha-mannosidosis store and excrete some unexpected oligosaccharides containing only one GlcNAc residue. Similarly, the action of ER/cytosolic mannosidase, followed by the action of the recently described human lysosomal alpha(1 → 6)-mannosidase, together explain why alpha-mannosidosis patients store and excrete large amounts of oligosaccharides that resemble biosynthetic intermediates, rather than partially degraded glycans. The relative contributions of the lysosomal and extra-lysosomal catabolic pathways can be derived by comparing the ratio of trisaccharide Man beta (1 → 4)GlcNAc beta (1 → 4)GlcNAc to disaccharide Man beta (1 → 4)GlcNAc accumulated in tissues from goats with beta-mannosidosis. A similar determination in human beta-mannosidosis patients is not possible because the same intermediate, Man beta (1 → 4)-GlcNAc is a product of both pathways. Based on inhibitor studies with pyranose and furanose analogues, alpha-mannosidases may be divided into two groups. Those in Class 1 are (1 → 2)-specific enzymes like Golgi mannosidase I, whereas those in Class 2, like lysosomal alpha-mannosidase, can hydrolyse (1 → 2), (1 → 3) and (1 → 6) linkages. A similar classification has been derived from protein sequence homologies. It is possible to speculate about their probable evolution from two primordial genes. The first would have been a Class 1 ER enzyme involved in the degradation of glycans on incompletely assembled or malfolded glycoproteins. The second would have been a Class 2 lysosomal enzyme responsible for turnover. Later, other alpha-mannosidases, with new processing or catabolic functions, would have developed from these, by loss or gain

of critical insertion or retention sequences, to yield the full complement of alpha-mannosidases known today (Glycobiology 1994 Oct;4(5):551-66). Defects in the lysosomal alpha-mannosidase gene cause lysosomal alpha-mannosidosis (AM), a lysosomal storage disease characterized by the accumulation of unbranched oligo-saccharide chains. Depending on the clinical findings at the age of onset, a severe infantile (type I) and a mild juvenile (type II) form of alpha-mannosidosis are recognized. Furthermore, variability in clinical expression of the disease is seen within each type. Some of the disease features are: susceptibility to infection, vomiting, coarse features, macroglossia, flat nose, large clumsy ears, widely spaced teeth, large head, big hands and feet, tall stature, slight hepatosplenomegaly, muscular hypotonia, lumbar gibbus, radiographic skeletal abnormalities, dilated cerebral ventricles, lenticular opacities, hypogammaglobulinemia, 'storage cells' in the bone marrow, and vacuolated lymphocytes in the bone marrow and blood.

The disclosed NOV10 nucleic acid of the invention encoding a Alpha-mannosidase-like protein includes the nucleic acid whose sequence is provided in Table 10A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 10A while still encoding a protein that maintains its Alpha-mannosidase-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 2 percent of the bases may be so changed.

The disclosed NOV10 protein of the invention includes the Alpha-mannosidase-like protein whose sequence is provided in Table 10B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 10B while still encoding a protein that maintains its Alpha-mannosidase-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 1 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the alpha-mannosidase-like protein and the NOV10 protein disclosed herein suggest that this alpha-mannosidase-like protein may have important structural and/or physiological functions characteristic of the mannosidase protein family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These applications include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

The NOV10 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from alpha-mannosidosis, beta-mannosidosis, other storage disorders, peroxisomal disorders such as zellweger syndrome, infantile refsum disease, rhizomelic chondrodysplasia (chondrodysplasia punctata, rhizomelic), and hyperpipecolic acidemia and other diseases, disorders and conditions of the like. Since mannosidoses are found not only in humans, but also in animals, the nucleic acids and proteins of the this invention may be useful in treating animals with mannosidoses or other storage diseases, and other diseases, disorders and conditions of the like. Additionally, the compositions of the present invention may have efficacy for treatment of patients suffering from conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors.. The NOV10 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV10 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV10 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV10 epitope is from about amino acids 5 to 20. In another embodiment, the

comtemplated NOV10 epitope is from about amino acids 40 to 80. In further embodiments, the contemplated NOV10 epitope is from about amino acids 110 to 180, from about amino acids 200 to 230, from about amino acids 300 to 370, from about amino acids 375 to 450, from about amino acids 650 to 680, from about amino acids 690 to 770, from about amino acids 790 to 820, from about amino acids 850 to 880, or from about amino acids 900 to 920. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV11

NOV11 includes three novel C1q-related factor-like proteins disclosed below. The disclosed sequences have been named NOV11a, NOV11b, and NOV11c. Single nucleotide polymorphism data is discussed below in Example 4.

NOV11a

A disclosed NOV11a nucleic acid of 805 nucleotides (also referred to as GM57107065_da1) encoding an C1q-related factor-like protein is shown in Table 11A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 83-85 and ending with a TGA codon at nucleotides 797-799. Putative untranslated regions are upstream from the initiation codon and downstream from the termination codon.

Table 11A. NOV11a nucleotide sequence (SEQ ID NO:27).

```
GAGTGAGGAAGATTTGCTGGCCCTGGCAGCGTCGCGGCTGAGCCGCCGCAAGAGGGTGGCGGGCGCGGCCGTCGGAGTGG
CCATGGTGCTGCTGCTGCTGGTGGCCATCCCGCTGCTGGTGCACAGCTCCCGCGGGCCAGCGCACTACGAGATGCTGGGT
CGCTGCCGCATGGTGTGCGACCCGCATGGGCCCCGTGGCCCTGGTCCGGACGGCGCGCCTGCTTCCGTGCCCCCCTTCCC
GCCAGGCGCCAAGGGAGAGGTGGGCCGGTGCGGGAAAGCAGGCCTGAGGGGGCCCCCTGGACCACCAGGTCCAAGAGGGC
CCCCAGGAGAACCCGGCAGGCCAGGCCCCCCGGGCCCTCCCGGTCCAGGTCCGGGCGGGGTGGCGCCCGCTGCCGGCTAC
GTGCCTCGCATTGCTTTCTACGCGGGCCTGCGGCGGCCCCACGAGGGTTACGAGGTGCTGCGCTTCGACGACGTGGTGAC
CAACGTGGGCAACGCCTACGAGGCAGCCAGCGGCAAGTTTACTTGCCCCATGCCAGGCGTCTACTTCTTCGCTTACCACG
TGCTCATGCGCGGCGGCGACGGCACCAGCATGTGGGCCGACCTCATGAAGAACGGACAGGTCCGGGCCAGCGCCATTGCT
CAGGACGCGGACCAGAACTACGACTACGCCAGCAACAGCGTCATTCTGCACCTGGACGTGGGCGACGAGGTCTTCATCAA
GCTGGACGGCGGGAAAGTGCACGGCGGCAACACCAACAAGTACAGCACCTTCTCCGGCTTCATCATCTACCCCGACTGAG
CCGGC
```

In a search of public sequence databases, the NOV11a nucleic acid, located on chromsome 12, has 565 of 787 bases (71%) identical to a C1q- related factor mRNA from *Homo sapiens*, (GENBANK-ID: AF095154) ($E = 9.9e^{-68}$). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV11a polypeptide (SEQ ID NO:28) encoded by SEQ ID NO:27 has 238 amino acid residues and is presented in Table 11B using the one-letter amino acid code.

Signal P, Psort and/or Hydropathy results predict that NOV11a has a signal peptide and is likely to be localized extracellularly with a certainty of 0.5374. In other embodiments, NOV11a is also likely to be localized to the microbody (peroxisome) with a certainty of 0.1111, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, and to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV11a is between positions 15 and 16: VHS-SR.

Table 11B. Encoded NOV11a protein sequence (SEQ ID NO:28).

```
MVLLLLVAIPLLVHSSRGPAHYEMLGRCRMVCDPHGPRGPGPDGAPASVPPFPPGAKGEVGRCGKAGLRGPP
GPPGPRGPPGEPGRPGPPGPPGPGPGGVAPAAGYVPRIAFYAGLRRPHEGYEVLRFDDVVTNVGNAYEAASG
KFTCPMPGVYFFAYHVLMRGGDGTSMWADLMKNGQVRASAIAQDADQNYDYASNSVILHLDVGDEVFIKLDG
GKVHGGNTNKYSTFSGFIIYPD
```

A search of sequence databases reveals that the NOV11a amino acid sequence has 184 of 258 amino acid residues (71%) identical to, and 198 of 258 amino acid residues (76%) similar to, the 258 amino acid residue C1q-related factor precursor protein from *Homo sapiens* (075973) ($E = 9.1\ e^{-91}$). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV11a is specifically expressed in the following tissues: brain, heart, testis, kidney, thyroid, prostate, fetal kidney, fetal skletal. It shows increased expression in cancer cell lines derived from the following tissue: colon, kidney, ovary, skin, brain. It is highly upregulated in IFN-gamma treated endothelial cells. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources and Taqman results.

NOV11b

A disclosed NOV11b nucleic acid of 805 nucleotides (also referred to as CG54503-02) encoding a novel C1q-related factor-like protein is shown in Table 11C. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 83-85 and ending with a TGA codon at nucleotides 797-799. Putative untranslated regions are underlined and are found upstream from the initiation codon and downstream from the termination codon.

Table 11C. NOV11b nucleotide sequence (SEQ ID NO:29).

```
GAGTGAGGAAGATTTGCTGGCCCTGGCAGCGTCGCGGCTGAGCCGCCGCAAGAGGGTGGCGGGCGCGGCCGTCGGAGTGG
CCATGGTGCTGCTGCTGCTGGTGGCCATCCCGCTGCTGGTGCACAGCTCCCGCGGGCCAGCGCACTACGAGATGCTGGGT
CGCTGCCGCATGGTGTGCGACCCGCATGGGCCCCGTGGCCCTGGTCCGGACGGCGCGCCTGCTTCCGTGCCCCCCTTCCC
GCCAGGCGCCAAGGGAGAGGTGGGCCGGCGCGGGAAAGCAGGCCTGCGGGGGCCCCCTGGACCACCAGGTCCAAGAGGGC
CCCCAGGAGAACCCGGCAGGCCAGGCCCCCCGGGCCCTCCCGGTCCAGGTCCGGGCGGGGTGGCGCCCGCTGCCGGCTAC
GTGCCTCGCATTGCTTTCTACGCGGGCCTGCGGCGGCCCCACGAGGGTTACGAGGTGCTGCGCTTCGACGACGTGGTGAC
CAACGTGGGCAACGCCTACGAGGCAGCCAGCGGCAAGTTTACTTGCCCCATGCCAGGCGTCTACTTCTTCGCTTACCACG
TGCTCATGCGCGGCGGCGACGGCACCAGCATGTGGGCCGACCTCATGAAGAACGGACAGGTCCGGGCCAGCGCCATTGCT
CAGGACGCGGACCAGAACTACGACTACGCCAGCAACAGCGTCATTCTGCACCTGGACGTGGGCGACGAGGTCTTCATCAA
GCTGGACGGCGGGAAAGTGCACGGCGGCAACACCAACAAGTACAGCACCTTCTCCGGCTTCATCATCTACCCCGACTGAG
CCGGC
```

In a search of public sequence databases, the NOV11a nucleic acid, located on chromsome 17q21, has 565 of 787 bases (71%) identical to a C1q- related factor mRNA from *Homo sapiens*, (GENBANK-ID: AF095154) ($E = 1.9e^{-68}$). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV11b polypeptide (SEQ ID NO:30) encoded by SEQ ID NO:29 has 238 amino acid residues and is presented in Table 11D using the one-letter amino acid code. The SignalP, Psort and/or Hydropathy profile for NOV11b predict that this sequence has a signal peptide and is likely to be localized extracellularly with a certainty of 0.5374, as expected by a protein similar to the C1q complement component. In other embodiments, NOV11b is also likely to be localized to the microbody (peroxisome) with a certainty of 0.1199, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, and to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV11b is between positions 15 and 16: VHS-SR.

Table 11D. Encoded NOV11b protein sequence (SEQ ID NO:30).

```
MVLLLLVAIPLLVHSSRGPAHYEMLGRCRMVCDPHGPRGPGPDGAPASVPPFPPGAKGEVGRRGKAGLRGPP
GPPGPRGPPGEPGRPGPPGPPGPGPGGVAPAAGYVPRIAFYAGLRRPHEGYEVLRFDDVVTNVGNAYEAASG
KFTCPMPGVYFFAYHVLMRGGDGTSMWADLMKNGQVRASAIAQDADQNYDYASNSVILHLDVGDEVFIKLDG
GKVHGGNTNKYSTFSGFIIYPD
```

A search of sequence databases reveals that the NOV11b amino acid sequence has 184 of 258 amino acid residues (71%) identical to, and 198 of 258 amino acid residues (76%) similar to, the 258 amino acid residue C1q-related factor precursor protein from *Homo sapiens* (075973) ($E = 7.1\ e^{-91}$). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV11b is expressed in at least some of the following tissues: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney,

lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus, right cerebellum. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

The disclosed NOV11a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 11E.

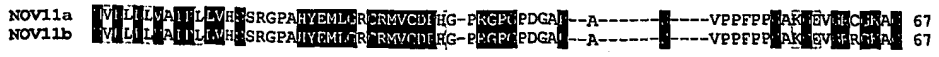
Table. 11E. BLAST results for NOV11a

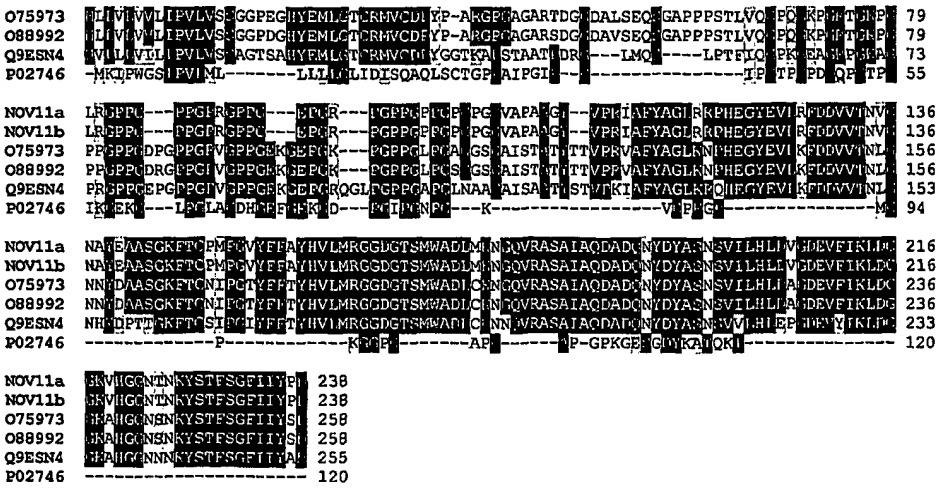
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
Ptnr: SWISSPROT-ACC: 075973	C1q-related factor precursor - Homo sapiens	258	184/258 (71%)	198/258 (76%)	9.1e-91
ptnr:SWISSPROT-ACC:O88992	C1q-related factor precursor - Mus musculus	258	156/216 (72%)	166/216 (76%)	1.8e-78
ptnr:SWISSPROT-ACC:Q9ESN4	Gliacolin precursor - Mus musculus	155	153/209 (73%)	165/209 (78%)	1.3e-77
ptnr:SWISSPROT-ACC:P02746	Complement C1q subcomponent	251	90/239 (37%)	124/239 (51%)	1.3e-29
ptnr:TREMBLNEW-ACC:AAH08983	COMPLEMENT COMPONENT 1	253	90/239 (37%)	124/239 (51%)	1.3e-29

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 11F. In the ClustalW alignment of the NOV11 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 11F. ClustalW Analysis of NOV11

1) NOV11a (SEQ ID NO:28)
2) NOV11b (SEQ ID NO:30)
3) ptnr: C1q-related factor precursor - Homo sapiens (SEQ ID NO:77)
4) ptnr: C1q-related factor precursor - Mus musculus (SEQ ID NO:78)
5) ptnr: Gliacolin precursor - Mus musculus (SEQ ID NO:79)
6) ptnr: Complement C1q subcomponent (SEQ ID NO:80)





Tables 11E-11F list the domain descriptions from DOMAIN analysis results against NOV11. This indicates that the NOV11 sequence has properties similar to those of other proteins known to contain this domain.

Table 11E. Domain Analysis of NOV11

gnl|Smart|smart00110, C1Q, Complement component C1q domain.; Globular domain found in many collagens and eponymously in complement C1q. When part of full length proteins these domains form a 'bouquet' due to the multimerization of heterotrimers. The C1q fold is similar to that of tumour necrosis factor. (SEQ ID NO:104)
CD-Length = 132 residues, 99.2% aligned
Score = 113 bits (283), Expect = 1e-26

```
Query:  108  PRIAFYAGL--RRPHEGYEVLRFDDVVTNVGNAYEAASGKFTCPMPGVYFFAYHVLMRGG  165
             || ||       ||    + +||| |+ |    |+ ++|||||+||||+|+||+  +
Sbjct:  2    PRSAFSVIRSTNRPPPPGQPVRFDKVLYNQQGHYDPSTGKFTCPVPGVYYFSYHIESK--  59

Query:  166  DGTSMWADLMKNGQVRASAIAQDADQNYDYASNSVILHLDVGDEVFIKLDGGKVHG-GNT  224
              | ++   |||||         +     |  ||   +| |   ||+|+++||   |
Sbjct:  60   -GRNVKVSLMKNGIQVMRECDEYQKGLYQVASGGALLQLRQGDQVWLELDDKKNGLYAGE  118

Query:  225  NKYSTFSGFIIYPD  238
                ||||||+++||
Sbjct:  119  EVDSTFSGFLLFPD  132
```

Table 11F. Domain Analysis of NOV11

gnl|Pfam|pfam00386, C1q, C1q domain. C1q is a subunit of the C1 enzyme complex that activates the serum complement system. (SEQ ID NO:112)
CD-Length = 125 residues, 100.0% aligned
Score = 102 bits (253), Expect = 3e-23

```
Query:  111  AFYAGLR-RPHEGYEVLRFDDVVTNVGNAYEAASGKFTCPMPGVYFFAYHVLMRGGDGTS  169
             || |    ||    + + ||+|+ |    |+ |+|||||+||+|+| +||  +   ||+
Sbjct:  1    AFTAIRSTRPPAPGQPVIFDEVLYNQQGHYDPATGKFTCPVPGLYYFNFHVSSK---GTN  57
```

```
Query:  170  MWADLMKNGQVRASAIAQDADQNYDYASNSVILHLDVGDEVFIKLDGGKVHG--GNTNKY  227
             +   ||+||     |   + |   |  ||   +| |  || |+++||  + +|  |    +
Sbjct:  58   VCVSLMRNGVPVMSFCDEYAKGTYQVASGGAVLQLRQGDRVWLELDDKQTNGLLGGEGVH  117

Query:  228  STFSGFII  235
             | ||||++
Sbjct:  118  SVFSGFLL  125
```

The first component of complement system is a calcium-dependent complex of the 3 subcomponents C1q, C1r, and C1s. Subcomponent C1q binds to immunoglobulin complexes with resulting serial activation of C1r (enzyme), C1s (proenzyme) and the other 8 components of complement. It contains collagen like domains. It has been shown that fibronectin binds to C1q in the same manner that it binds collagen. A major function of the fibronectins is in the adhesion of cells to extracellular materials such as solid substrata and matrices. Because fibronectin stimulates endocytosis and promotes the clearance of particulate material from the circulation, the results suggest that fibronectin functions in the clearance of C1q-coated material such as immune complexes or cellular debris. Many examples of deficiencies of C1q have been reported, most of them associated with systemic lupus erythematosus or glomerulonephritis.

The complement system plays a paradoxical role in the development and expression of autoimmunity in humans. The activation of complement in SLE contributes to tissue injury. In contrast, inherited deficiency of classic pathway components, particularly C1q, is probably associated with the development of SLE. This leads to the hypothesis that a physiologic action of the early part of the classic pathway protects against the development of SLE and implies that C1q may play a key role in this respect. C1q-deficient (C1qa-/-) mice have been shown to have increased mortality and higher titers of autoantibodies, compared with strain-matched controls. Of the C1qa-/- mice, 25% have been shown to have glomerulonephritis with immune deposits and multiple apoptotic cell bodies. Among mice without glomerulonephritis, there were significantly greater numbers of glomerular apoptotic bodies in C1q-deficient mice compared with controls. The phenotype associated with C1q deficiency was modified by background genes. These findings are compatible with the hypothesis that C1q deficiency causes autoimmunity by impairment of the clearance of apoptotic cells.

The C1q-related factor is a recently discovered protein which has homology to C1q. Since this is a relatively new discovery, very little is known about its function. But conclusions could clearly be derived from it expression pattern and it homology to C1q. Based on its expression pattern it has been suggested that this protein may be involved in motor function.

The functions of C1q has been described above and include role in binding to immunoglobulin complexes, cell adhesion, autoimmunity and apoptosis, among others.

The disclosed NOV11 nucleic acid of the invention encoding a C1q-related factor-like protein includes the nucleic acid whose sequence is provided in Table 11A, 11C, or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 11A or 11C while still encoding a protein that maintains its C1q-related factor-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 29 percent of the bases may be so changed.

The disclosed NOV11 protein of the invention includes the C1q-related factor-like protein whose sequence is provided in Table 11B or 11D. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 11B or 11D while still encoding a protein that maintains its C1q-related factor-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 29 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the C1q-related factor-like protein and nucleic acid disclosed herein suggest that this C1q-related factor may have important structural and/or physiological functions characteristic of the C1q family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

The nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. Based on the TaqMan data, the compositions of the present invention, will have efficacy for treatment of patients suffering from: cancer of the colon, kidney, ovary, skin and brain. Since it is over expressed in cell lines derived from these tissues it can also be used as a diagnostic marker for cancer in these tissues. The expression of the novel gene of this invention upon activation of HUVEC and the homology of the novel protein of this invention to C1q may indicate that it is secreted by endothelial cells in areas of inflammtion where Th1 cells are inflitrating the inflammation site such as Rheumatoid Arthritis and Inflammatory Bowel Disease. Based on its homology to C1q, the novel protein could be either pro-inflammatory activating the complement cascade and be a useful target for a monoclonal antibody to block this effect. Alternatively, this protein may act as a competitor of C1q and so act to down regulate complement mediated damage of endothelial cells. In this case it could be used as a protein therapeutic. IFN gamma also induces production of this protein by airway epithelilial cell lines NCI-H292 and dermal fibroblasts indicating again that it may play a role in Th1 inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases and psoriasis and other diseases, disorders and conditions of the like. Because of its high homology to C1q-related factor, this novel protein may also play a role in disorders of the nervous system involved in motor function.

Based on its homology to C1q, the novel protein of invention may also play a role in the pathogenesis of systemic lupus erythematosus and glomerulonephritis and therefore could be used for detection and treatment of these diseases. Thus this protein may be involved in autoimmunity. Since the novel protein of invention has a Collagen triple helix repeat domain , it is likely that this protein may be involved in collagen related disorders and processes such as but not limited to osteogenesis, rheumatoid arthritis and osteoarthritis.

Finally, presence of somatotropin-like domain in the novel protein of invention suggests that it may have somatotropin (growth hormone) like function and behave as a growth hormone and be useful in control of growh and development/differentiation related functions such as but not limited maturation, lactation and puberty. Because of the involvement of growth hormone in many different physiologic functions, the novel protein may be involved in causing osteoporosis, obesity, aging and reproductive malfunction and hence could be used in treatment and/or diagnosis of these disorders.

The NOV11 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV11 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV11 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV11 epitope is from about amino acids 20 to 120. In another embodiment, the comtemplated NOV11 epitope is from about amino acids 130 to 150. In further embodiments, the contemplated NOV11 epitope is from about amino acids 170 to 210, or from about amino acids 220 to 240. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV12

A disclosed NOV12 nucleic acid of 5895 nucleotides (also referred to as SC132340676_A) encoding an plexin-1-like protein is shown in Table 12A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 77-79 and ending with a TGA codon at nucleotides 5798-5800. The putative untranslated regions are underlined and are upstream from the initiation codon and downstream from the termination codon in Table 12A. The start and stop codons are in bold letters.

Table 12A. NOV12 nucleotide sequence (SEQ ID NO:31).

CAGGGCTGAAGCTCCTGGCACCATGATGCTCACCCCAGCAGGACCAGAGCACCGAGGCCCAAGGCCCCAGCCTGCC**ATG**C
CGCTGCCACCGCGGAGCCTGCAGGTGCTCCTGCTGCTGCTGCTGTTGCTGCTGCTGCCGGGCATGTGGGCTGAGGCA
GGCTTGCCCAGGGCAGGCGGGGGTTCACAGCCCCCCTTCCGCACCTTCTCGGCCAGCGACTGGGGCCTCACCCACCTAGT
GGTGCATGAGCAGACAGGCGAGGTGTATGTGGGCGCAGTGAACCGCATCTATAAGCTGTCGGGGAACCTGACACTGCTGC
GGGCCCACGTCACGGGCCCTGTGGAGGACAACGAGAAGTGCTACCCGCCGCCCAGCGTGCAGTCCTGCCCCCACGGCCTG
GGCAGTACTGACAACGTCAACAAGCTGCTGCTGCTGGACTATGCCGCTAACCGCCTGCTGGCCTGTGGCAGCGCCTCCCA
GGGCATCTGCCAGTTCCTGCGTCTGGACGATCTCTTCAAACTGGGTGAGCCACACCACCGTAAGGAGCACTACCTGTCCA
GCGTGCAGGAGGCAGGCAGCATGGCGGGCGTGCTCATTGCCGGGCCACCGGGCCAGGGCCAGGCCAAGCTCTTCGTGGGC
ACACCCATCGATGGCAAGTCCGAGTACTTCCCCACACTGTCCAGCCGTCGGCTCATGGCCAACGAGGAGGATGCCGACAT
GTTCGGCTTCGTGTACCAGGATGAGTTTGTGTCATCACAGCTCAAGATCCCTTCGGACACGCTGTCCAAGTTCCCGGCCT
TTGACATCTACTATGTGTACAGCTTCCGCAGCGAGCAGTTTGTCTACTACCTCACGCTGCAGCTAGACACACAGCTGACC
TCGCCTGATGCCGCCGGCGAGCACTTCTTCACGTCCAAGATCGTGCGGCTCTGTGTGGACGACCCCAAATTCTACTCGTA
CGTTGAGTTCCCCATTGGCTGCGAGCAGGCGGGTGTGGAGTACCGCCTGGTGCAGGATGCCTACCTGAGCCGGCCCGGCC
GTGCCCTGGCCCACCAGCTGGGCCTGGCTGAGGACGAGGACGTGCTGTTCACTGTGTTCGCCCAGGGCCAGAAGAACCGC
GTGAAGCCACCAAAGGAGTCAGCACTGTGCCTGTTCACGCTCAGGGCCATCAAGGAGAAGATTAAGGAGCGCATCCAGTC
CTGCTACCGTGGTGAGGGCAAGCTCTCCCTGCCGTGGCTGCTCAACAAGGAGCTGGGCTGCATCAACTCGCCCCTGCAGA

TCGATGACGACTTCTGCGGGCAGGACTTCAACCAGCCCCTGGGGGGCACAGTCACCATTGAGGGGACGCCCCTGTTCGTG
GACAAGGATGATGGCCTGACCGCCGTGGCTGCCTATGACTATCGGGGCCGCACTGTGGTATTCGCCGGCACGCGAAGTGG
CCGCATCCGCAAGATCCTGGTGGACCTCTCAAACCCCGGTGGCCGGCCTGCCCTGGCCTACGAGAGCGTCGTGGCCCAGG
AGGGCAGCCCCATCCTGCGAGACCTCGTCCTCAGCCCCAACCACCAGTACCTCTACGCCATGACCGAGAAGCAGGTGACG
CGGGTGCCTGTGGAGAGCTGTGTGCAGTACACGTCCTGTGAGCTGTGTCTGGGGTCACGGGACCCCCACTGTGGCTGGTG
TGTCCTGCACAGCATGTGCTCGCGGCGGGACGCCTGTGAGCGAGCAGACGAGCCCCAGCGCTTTGCTGCGGACCTGCTGC
AGTGTGTGCAGCTGACTGTGCAGCCCCGCAATGTGTCTGTCACCATGTCCCAGGTCCCAGTACTTGTGCTGCAGGCCTGG
AACGTGCCTGACCTCTCAGCTGGCGTCAACTGCTCCTTCGAGGACTTCACGGAATCTGAGAGCGTCCTGGAGGATGGCCG
GATCCACTGCCGCTCACCCTCCGCCCGGGAGGTGGCGCCCATCACGCGGGGCCAGGGTGAGGGAGACCAGCGGGTGGTGA
AACTCTACCTAAAGTCCAAGGAGACAGGGAAGAAGTTTGCGTCTGTGGACTTCGTCTTCTACAACTGCAGCGTCCACCAG
TCGAGCTGCCTGTCCTGTGTCAACGGCTCCTTTCCCTGCCACTGGTGCAAATACCGCCACGTGTGCACACACAACGTGGC
TGACTGCGCCTTCCTGGAGGGCCGTGTCAACGTGTCTGAGGACTGCCCACAGATCCTGCCCTCCACGCAGATCTACGTGC
CAGTGGGAGTGGTAAAACCCATCACCCTGGCCGCACGGAACCTGCCACAGCCACAGTCAGGCCAGCGTGGATATGAGTGC
CTCTTCCACATCCCGGGCAGCCCGGCCCGTGTCACCGCCCTGCGCTTCAACAGCTCCAGCCTGCAGTGCCAGAATTCCTC
GTACTCCTACGAGGGGAACGATGTCAGCGACCTGCCAGTGAACCTGTCAGTCGTGTGGAACGGCAACTTTGTCATTGACA
ACCCACAGAACATCCAGGCGCACCTCTACAAGTGCCCGGCCCTGCGCGAGAGCTGCGGCCTCTGCCTCAAGGCCGACCCG
CGCTTCGAGTGCGGATGGTGCGTGGCCGAGCGCCGCTGCTCCCTGCGACACCACTGCGCTGCCGACACACCTGCATCGTG
GATGCACGCGCGTCACGGCAGCAGTCGCTGCACCGACCCCAAGATCCTCAAGCTGTCCCCCGAGACGGGCCCGAGGCAGG
GCGGCACGCGGCTCACTATCACAGGCGAGAACCTGGGCCTGCGATTCGAAGACGTGCGTCTGGGCGTGCGCGTGGGCAAG
GTGCTGTGCAGCCCTGTGGAGAGCGAGTACATCAGTGCGGAGCAGATCGTCTGTGAGATCGGGGACGCCAGCTCCGTGCG
TGCCCATGACGCCCTGGTGGAGGTGTGTGTGCGGGACTGCTCACCACACTACCGCGCCCTGTCACCCAAGCGCTTCACCT
TCGTGACACCAACCTTCTACCGTGTGAGCCCCTCCCGTGGGCCTCTGTCAGGGGGCACCTGGATTGGCATCGAGGGAAGC
CACCTGAACGCAGGCAGTGATGTGGCTGTGTCGGTCGGTGGCCGGCCCTGCTCCTTCTCCTGGTCCAGGAGGAACTCCCG
TGAGATCCGGTGCCTGACACCCCCCGGGCAGAGCCCTGGCAGCGCTCCCATCATCATCAACATCAACCGCGCCCAGCTCA
CCAACCCTGAGGTGAAGTACAACTACACCGAGGACCCCACCATCCTGAGGATCGACCCCGAGTGGAGCATCAACAGCGGT
GGGACCCTCCTGACGGTCACAGGCACCAACCTGGCCACTGTCCGTGAACCCCGAATCCGGGCCAAGTATGGAGGCATTGA
GAGGGAGAACTGCCTGGTGTACAATGACACCACCATGGTATGCCGCGCCCCGTCTGTGGCCAACCCTGTGCGCAGCCCAC
CAGAGCTGGGGGAGCGGCCGGATGAGCTGGGCTTCGTCATGGACAACGTGCGCTCCCTGCTTGTGCTCAACTCCACCTCC
TTCCTCTACTACCCTGACCCCGTACTGGAGCCACTCAGCCCCACTGGCCTGCTGGAGCTGAAGCCCAGCTCCCCACTCAT
CCTCAAGGGCCGGAACCTCTTGCCACCTGCACCCGGCAACTCCCGACTCAACTACACGGTGCTCATCGGCTCCACACCCT
GTACCCTCACCGTGTCGGAGACGCAACTGCTGTGCGAGGCGCCCAACCTCACTGGGCAGCACAAGGTCACGGTGCGTGCA
GGTGGCTTCGAGTTCTCGCCAGGGACACTGCAGGTGTACTCGGACAGCCTGCTGACGCTGCCTGCCATTGTGGGCATTGG
CGGAGGCGGGGGTCTCCTGCTGCTGGTCATCGTGGCTGTGCTCATCGCCTACAAGCGCAAGTCACGAGATGCTGACCGCA
CACTCAAGCGGCTGCAGCTCCAGATGGACAACCTGGAGTCCCGCGTGGCCCTCGAATGCAAGGAAGCCTTTGCAGAGCTG
CAGACAGACATCCACGAGCTGACCAATGACCTGGACGGTGCCGGCATCCCCTTCCTTGACTACCGGACATATGCCATGCG
GGTGCTCTTTCCTGGGATCGAGGACCACCCTGTGCTCAAGGAGATGGAGGTACAGGCCAATGTGGAGAAGTCGCTGACAC
TGTTCGGGCAGCTGCTGACCAAGAAGCACTTCCTGCTGACCTTCATCCGCACGCTGGAGGCACAGCGCAGCTTCTCCATG
CGCGACCGCGGGAATGTGGCCTCGCTCATCATGACGGCCCTGCAGGGCGAGATGGAATACGCCACAGGCGTGCTCAAGCA
GCTGCTTTCCGACCTCATCGAGAAGAACCTGGAGAGCAAGAACCACCCCAAGCTGCTACTGCGCCGGCCAACTGAGTCGG
TGGCAGAGAAGATGCTAACTAACTGGTTCACCTTCCTCTTGTATAAGTTCCTCAAGGAGTGCGCTGGGGAGCCGCTGTTC
ATGCTGTACTGCGCCATCAAGCAGCAGATGGAGAAGGGCCCCATTGACGCCATCACGGGTGAGGCACGCTACTCCCTGAG
TGAGGACAAGCTCATCCGGCAGCAGATTGACTACAAGACACTGACCCTGAACTGTGTGAACCCTGAGAATGAGAATGCAC
CTGAGGTGCCGGTGAAGGGGCTGGACTGTGACACGGTCACCCAGGCCAAGGAGAAGCTGCTGGACGCTGCCTACAAGGGC
GTGCCCTACTCCCAGCGGCCCAAGGCCGCGGACATGGACCTGGAGTGGCGCCAGGGCCGCATGGCGCGCATCATCCTGCA
GGACGAGGACGTCACCACCAAGATTGACAACGATTGGAAGAGGCTGAACACACTGGCTCACTACCAGGTGACAGACGGGT
CCTCGGTGGCACTGGTGCCCAAGCAGACGTCCGCCTACAACATCTCCAACTCCTCCACCTTCACCAAGTCCCTCAGCAGA
TACGAGAGCATGCTGCGCACGGCCAGCAGCCCCGACAGCCTGCGCTCGCGCACGCCCATGATCACGCCCGACCTGGAGAG
CGGCACCAAGCTGTGGCACCTGGTGAAGAACCACGACCACCTGGACCAGCGTGAGGGTGACCGCGGCAGCAAGATGGTCT
CGGAGATCTACTTGACACGGCTACTGGCCACCAAGCAGGGCACACTGCAGAAGTTTGTGGACGACCTGTTTGAGACCATC
TTCAGCACGGCACACCGGGGCTCAGCCCTGCCGCTGGCCATCAAGTACATGTTCGACTTCCTGGATGAGCAGGCCGACAA
GCACCAGATCCACGATGCTGACGTGCGCCACACCTGGAAGAGCAACTGCAGCCTGCCCCTGCGCTTCTGGGTGAACGTGA
TCAAGAACCCACAGTTTGTGTTCGACATTCACAAGAACAGCATCACGGACGCCTGCTTGTCGGTGGTGGCCCAGACCTTC
ATGGACTCCTGCTCCACCTCTGAGCACAAGCTGGGCAAGGACTCACCCTCCAACAAGCTGCTCTACGCCAAGGACATCCC
CAACTACAAGAGCTGGGTGGAGAGGAGGTACTATGCAGACATCGCCAAGATGCCAGCCATCAGCGACCAGGACATGAGTG
CGTATCTGGCTGAGCAGTCCCGCCTGCACCTGAGCCAGTTCAACAGCATGAGCGCCTTGCACGAGATCTACTCCTACATC
ACCAAGTACAAGGATGAGGTGCAGATCCTGGCAGCCCTGGAGAAGGATGAGCAGGCGCGGCGGCAGCGGCTGCGGAGCAA
GCTGGAGCAGGTGGTGGACACGATGGCCCTGAGCAGCTGAGCCCCAGCTGTGATCATCCAGCATGATGCAGCGTGAGGAC
AGCTGAGCAGGGACCGGGACAGCCCTCACCGCATGCGTGTGGAGTGTCCGGTGGT

In a search of public sequence databases, the NOV12 nucleic acid sequence, located on chromsome 8 has 2950 of 3362 bases (87%) identical to a plexin-1 mRNA from *Mus musculus*, (GENBANK-ID: D86948) (E = 0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV12 polypeptide (SEQ ID NO:32) encoded by SEQ ID NO:31 has 1925 amino acid residues and is presented in Table 12B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV12 contains a signal peptide and is likely to be localized in the plasma membrane with a certainty of 0.6000. In other embodiments, NOV12 is likely to be localized to the Golgi body with a certainty of 0.4000, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, or to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV12 is between positions 44 and 45: MWA-EA.

Table 12B. Encoded NOV12 protein sequence (SEQ ID NO:32).

```
MMLTPAGPEHRGPRPQPAMPLPPRSLQVLLLLLLLLLLLPGMWAEAGLPRAGGGSQPPFRTFSASDWGLTHL
VVHEQTGEVYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNVNKLLLLDYAANR
LLACGSASQGICQFLRLDDLFKLGEPHHRKEHYLSSVQEAGSMAGVLIAGPPGQGQAKLFVGTPIDGKSEYF
PTLSSRRLMANEEDADMFGFVYQDEFVSSQLKIPSDTLSKFPAFDIYYVYSFRSEQFVYYLTLQLDTQLTSP
DAAGEHFFTSKIVRLCVDDPKFYSYVEFPIGCEQAGVEYRLVQDAYLSRPGRALAHQLGLAEDEDVLFTVFA
QGQKNRVKPPKESALCLFTLRAIKEKIKERIQSCYRGEGKLSLPWLLNKELGCINSPLQIDDDFCGQDFNQP
LGGTVTIEGTPLFVDKDDGLTAVAAYDYRGRTVVFAGTRSGRIRKILVDLSNPGGRPALAYESVVAQEGSPI
LRDLVLSPNHQYLYAMTEKQVTRVPVESCVQYTSCELCLGSRDPHCGWCVLHSMCSRRDACERADEPQRFAA
DLLQCVQLTVQPRNVSVTMSQVPVLVLQAWNVPDLSAGVNCSFEDFTESESVLEDGRIHCRSPSAREVAPIT
RGQGEGDQRVVKLYLKSKETGKKFASVDFVFYNCSVHQSSCLSCVNGSFPCHWCKYRHVCTHNVADCAFLEG
RVNVSEDCPQILPSTQIYVPVGVVKPITLAARNLPQPQSGQRGYECLFHIPGSPARVTALRFNSSSLQCQNS
SYSYEGNDVSDLPVNLSVVWNGNFVIDNPQNIQAHLYKCPALRESCGLCLKADPRFECGWCVAERRCSLRHH
CAADTPASWMHARHGSSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVRVGKVLCSPVESEY
ISAEQIVCEIGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFVTPTFYRVSPSRGPLSGGTWIGIEGSHL
NAGSDVAVSVGGRPCSFSWSRRNSREIRCLTPPGQSPGSAPIIININRAQLTNPEVKYNYTEDPTILRIDPE
WSINSGGTLLTVTGTNLATVREPRIRAKYGGIERENCLVYNDTTMVCRAPSVANPVRSPPELGERPDELGFV
MDNVRSLLVLNSTSFLYYPDPVLEPLSPTGLLELKPSSPLILKGRNLLPPAPGNSRLNYTVLIGSTPCTLTV
SETQLLCEAPNLTGQHKVTVRAGGFEFSPGTLQVYSDSLLTLPAIVGIGGGGGLLLLVIVAVLIAYKRKSRD
ADRTLKRLQLQMDNLESRVALECKEAFAELQTDIHELTNDLDGAGIPFLDYRTYAMRVLFPGIEDHPVLKEM
EVQANVEKSLTLFGQLLTKKHFLLTFIRTLEAQRSFSMRDRGNVASLIMTALQGEMEYATGVLKQLLSDLIE
KNLESKNHPKLLLRRPTESVAEKMLTNWFTFLLYKFLKECAGEPLFMLYCAIKQQMEKGPIDAITGEARYSL
SEDKLIRQQIDYKTLTLNCVNPENENAPEVPVKGLDCDTVTQAKEKLLDAAYKGVPYSQRPKAADMDLEWRQ
GRMARIILQDEDVTTKIDNDWKRLNTLAHYQVTDGSSVALVPKQTSAYNISNSSTFTKSLSRYESMLRTASS
PDSLRSRTPMITPDLESGTKLWHLVKNHDHLDQREGDRGSKMVSEIYLTRLLATKQGTLQKFVDDLFETIFS
TAHRGSALPLAIKYMFDFLDEQADKHQIHDADVRHTWKSNCSLPLRFWVNVIKNPQFVFDIHKNSITDACLS
VVAQTFMDSCSTSEHKLGKDSPSNKLLYAKDIPNYKSWVERRYYADIAKMPAISDQDMSAYLAEQSRLHLSQ
FNSMSALHEIYSYITKYKDEVQILAALEKDEQARRQRLRSKLEQVVDTMALSS
```

A search of sequence databases reveals that the NOV12 amino acid sequence has 1820 of 1907 amino acid residues (95%) identical to, and 1859 of 1907 amino acid residues (97%) similar to, the 1894 amino acid residue plexin-1 protein from *Mus musculus* (P70206) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV12 is expressed in at least the following tissues: whole organism, brain, testis, trabecular Bone, lymph, germinal center B cells. In addition, NOV12 is predicted to be expressed in the following tissues because of the expression pattern of (GENBANK-ID: acc:AI255192) a closely related plexin-1 homolog in species *Mus musculus*: brain, testis.

The disclosed NOV12 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 12C.

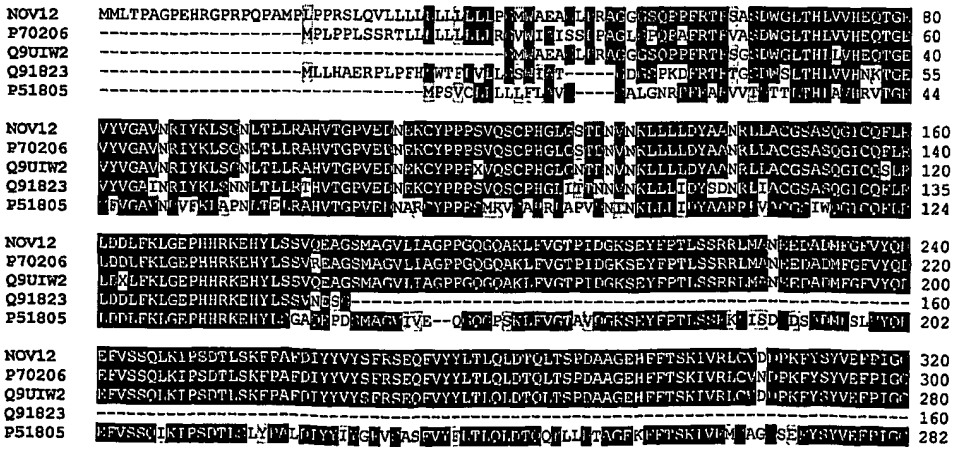
Table 12C. BLAST results for NOV12

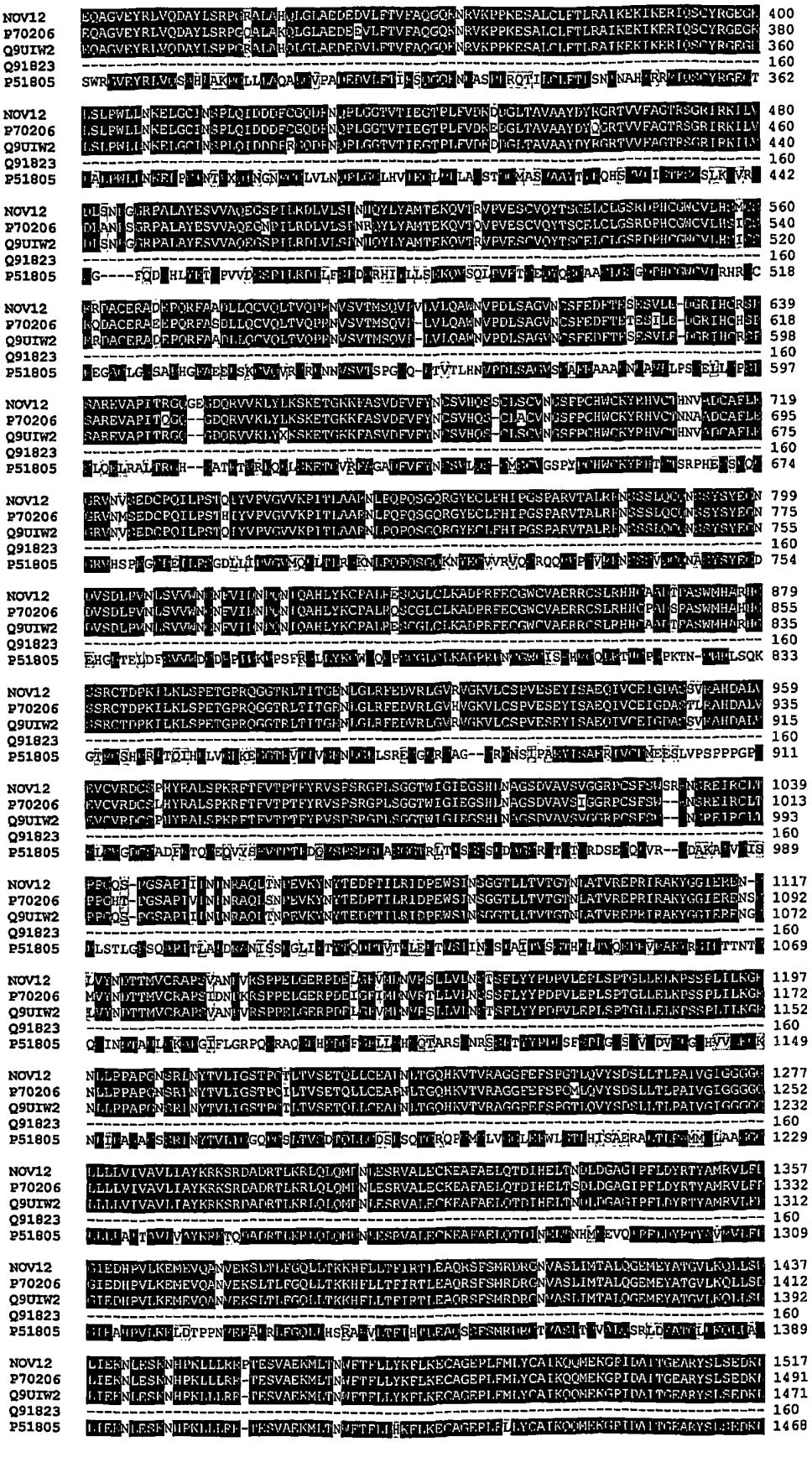
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
Ptnr:SPTREMBL-ACC:P70206	PLEXIN 1 - Mus musculus	1894	1820/1907 (95%)	1859/1907 (97%)	0.0
ptnr:SPTREMBL-ACC:Q9UIW2	NOV/PLEXIN-A1 PROTEIN - Homo sapiens	1754	1743/1762 (98%)	1746/1762 (99%)	0.0
ptnr:SPTREMBL-ACC:Q91823	PLEXIN PRECURSOR - Xenopus laevis	1905	1603/1893 (84%)	1730/1893 (91%)	0.0
ptnr:SWISSPROT-ACC:P51805	Plexin A3 precursor (Plexin 4)	1871	1252/1874 (66%)	1483/1874 (79%)	0.0
ptnr:SPTREMBL-ACC:P70208	PLEXIN 3 - Mus musculus	1872	1245/1874 (66%)	1478/1874 (78%)	0.0

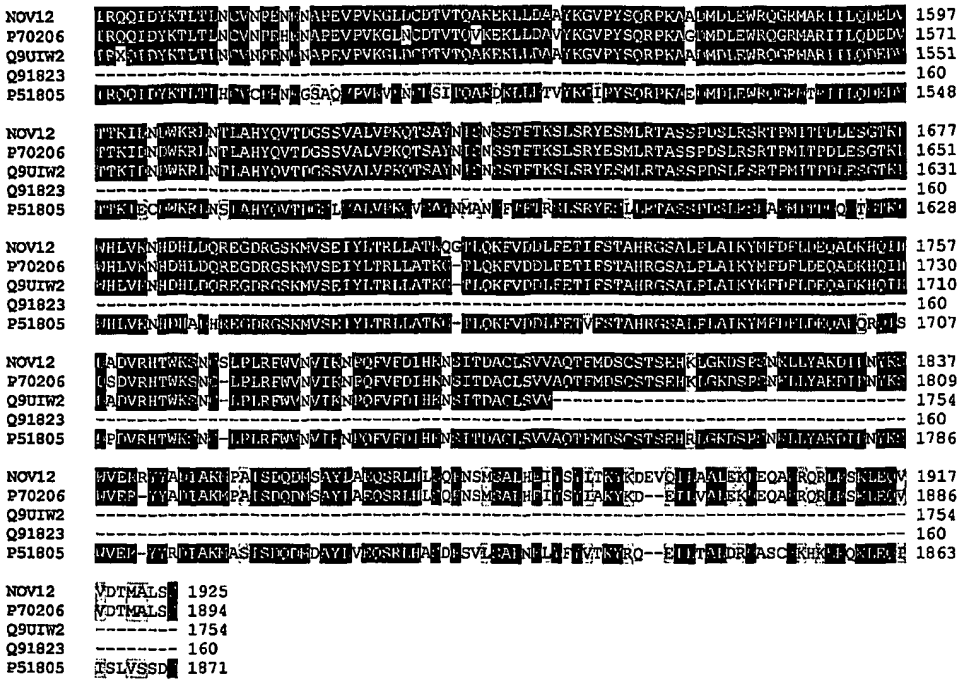
The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 12D. In the ClustalW alignment of the NOV12 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 12D. ClustalW Analysis of NOV12

1) NOV12 (SEQ ID NO:32)
2) ptnr: PLEXIN 1 - Mus musculus (SEQ ID NO:81)
3) ptnr: NOV/PLEXIN-A1 PROTEIN - Homo sapiens (SEQ ID NO:82)
4) ptnr: PLEXIN PRECURSOR - Xenopus laevis (SEQ ID NO:83)
5) ptnr: Plexin A3 precursor (Plexin 4) (SEQ ID NO:84)
6)




NOV12
P70206
Q9UIW2
Q91823
P51805



Tables 12E-12N list the domain descriptions from DOMAIN analysis results against NOV12. This indicates that the NOV12 sequence has properties similar to those of other proteins known to contain this domain.

Table 12E. Domain Analysis of NOV12

gnl|Smart|smart00630, Sema, semaphorin domain (SEQ ID NO:113)
CD-Length = 430 residues, 100.0% aligned
Score = 242 bits (618), Expect = 1e-64

```
Query:  69   LTHLVVHEQTGEVYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGS  128
             | +|++ |  | +|||| ||+| || ||       ||||  +  |     |
Sbjct:  1    LQNLLLDEDNGTLYVGARNRLYVLSLNLISEAEVKTGPVLSSPDCEEC--VSKGKDPP--  56

Query:  129  TDNVNK-LLLLDYAANRLLACGS-ASQGICQFLRLDDLFKLGEPHHRKEHYLSSVQEAGS  186
             || ||   ||||| |+ || ||+ | | +|+ + | +| +| |                +
Sbjct:  57   TDCVNFIRLLLDYNADHLLVCGTNAFQPVCRLINLGNLDRL-EVGRESGRGRCPFDPQHN  115

Query:  187  MAGVLIAGPPGQGQAKLFVGTPID--GKSEYFPTLSSRRLMANEEDADMFGFVYQDEFVS  244
             ||+ |       +|+|||  |  |          | | +                |
Sbjct:  116  STAVLVDG-------ELYVGTVADFSGSDPAIYRSLSVRRLKGTSG-------PSLRTVL  161

Query:  245  SQLKIPSDTLSKFPAFDIYYVYSFRSEQFVYYLTLQLDTQLTSPDAAGEHFFTSKIVRLC  304
             +  +         +  +||+| |  |||+       +     |         |++ |+|
Sbjct:  162  YDSRWLN---------EPNFVYAFESGDFVYF----FFRETAVEDENCGKAVVSRVARVC  208

Query:  305  VDD---------PKFYSYVEFPIGC---EQAGVEYRLVQDAYLSRPGRALAHQLGLAEDED  353
              +|          |+ |+++  + |    +    +  +| |+|    |          +| +|
Sbjct:  209  KNDVGGPRSLSKKWTSFLKARLECSVPGEFPFYFNELQAAFLLPAG---------SESDD  259

Query:  354  VLFTVFAQGQKNRVKPPKESALCLFTLRAIKEKIKERIQSCYRGEGKLSL----PWLLNK  409
             ||+ ||+         |   ||+| |+|  |      | + |  | +            +
Sbjct:  260  VLYGVFSTS----SNPIPGSAVCAFSLSDINAVFNEPFKECETGNSQWLPYPRGLVPFPR  315
```

```
Query:  410  ELGCINSPLQI----DDDFC-GQDFNQPLGGTVTIEGTPLFV--DKDDGLTAVAA----Y  458
Sbjct:  316  PGTCPNTPLSSKDLPDDVLNFIKTHPLMDEVVQPLTGRPLFVKTDSNYLLTSIAVDRVRT  375

Query:  459  DYRGRTVVFAGTRSGRIRKILVDLSNPGGRPALAYESVVAQEGSPILRDLVLSPNH  514
Sbjct:  376  DGGNYTVLFLGTSDGRILKVVLSRSSSSSESVVLEEISVFDPGSPV-SDLVLSPKK  430
```

Table 12F. Domain Analysis of NOV12

gnl|Pfam|pfam01403, Sema, Sema domain. The Sema domain occurs in semaphorins, which are a large family of secreted and transmembrane proteins, some of which function as repellent signals during axon guidance. Sema domains also occur in the hepatocyte growth factor receptor. (SEQ ID NO:114)
CD-Length = 433 residues, 99.5% aligned
Score = 171 bits (432), Expect = 5e-43

```
Query:  69   LTHLVVHEQTGEVYVGAVNRIYKLSGN----LTLLRAHVTGPVEDNEKCYPPPSVQSCPH  124
Sbjct:  1    FVTLLLDEDRGRLYVGARNRVYVLNLEDLSEVLNLKTGWPGSCETCEECNMKGKSP----  56

Query:  125  GLGSTDNVN-KLLLLDYAANRLLACGS-ASQGICQFLRLDDLFKLGEPHHRKEHYLSSVQ  182
Sbjct:  57   ---LTECTNFIRVLQAYNDTHLYVCGTNAFQPVCTLINLGDLFSLDVDNEEDGCGDCPYD  113

Query:  183  EAGSMAGVLIAGPPGQGQAKLFVGTPIDGKSEYFPTLSSRRLMANEEDADMFGFVYQDEF  242
Sbjct:  114  PLGNTTSVLVQG------GELYSGTVID------FSGRDPSIRRLLGSHDGLRTEFHD--  159

Query:  243  VSSQLKIPSDTLSKFPAFDIYYVYSFRSEQFVYYLTLQLDTQLTSPDAAGEHFFTSKIVR  302
Sbjct:  160  -SKWLNLPNFVD----SYPIHYVHSF-SDDKVYF----FFRETAVEDSNCKTIH-SRVAR  208

Query:  303  LCVDDPKFYSYVEFPIGC----------EQAGVEYRLVQDAYLSRPGRALAHQLGLA  349
Sbjct:  209  VCKNDPGGRSYLELNKWTTFLKARLNCSIPGEGTPFYFNELQAAFVLPTG---------A  259

Query:  350  EDEDVLFTVFAQGQKNRVKPPKESALCLFTLRAIKE--KIKERIQSCYRGEGKLSLPWLL  407
Sbjct:  260  DTDPVLYGVFTTS----SNSSAGSAVCAFSMSDINQVFEGPFKHQSPNSKWLPYRGKVPQ  315

Query:  408  NKELGCINSP-LQIDDDFCGQDFNQPLGGTVT--IEGTPLFVDKDDG--LTAVA-----A  457
Sbjct:  316  PRPGQCPNASGLNLPDDTLNFIRCHPLMDEVVPPLHNVPLFVGQSGNYRLTSIAVDRVRA  375

Query:  458  YDYRGRTVVFAGTRSGRIRKILVDLSNPGGR---PALAYESVVAQEGSPILRDLVLS  511
Sbjct:  376  GDGQIYTVLFLGTDDGRV-LKQVVLSRSSSASYLVVVLEESLVFPDGEPVQRMVISS  431
```

Table 12G. Domain Analysis of NOV12

gnl|Pfam|pfam01833, TIG, IPT/TIG domain. This family consists of a domain that has an immunoglobulin like fold. These domains are found in cell surface receptors such as Met and Ron as well as in intracellular transcription factors where it is involved in DNA binding. (SEQ ID NO:115)
CD-Length = 85 residues, 100.0% aligned
Score = 78.2 bits (191), Expect = 4e-15

```
Query:  983   PTFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFSWSRRNSREIRCLTPPG  1042
Sbjct:  1     PVITSISPSSGPLSGGTEITITGSNLGSGEDIKVTFGGTECDV--VSQEASQIVCKTPPY  58

Query:  1043  QSPGSAPIIININRAQLTNPEVKYNYT  1069
Sbjct:  59    ANGGPQPVTVSLDGGGLSSSPVTFTYV  85
```

Table 12H. Domain Analysis of NOV12

gnl|Pfam|pfam01833, TIG, IPT/TIG domain. This family consists of a domain that has an immunoglobulin like fold. These domains are found in cell surface receptors such as Met and Ron as well as in intracellular transcription factors where it is involved in DNA binding. (SEQ ID NO:115)
CD-Length = 85 residues, 100.0% aligned
Score = 60.1 bits (144), Expect = 1e-09

```
Query:  886   PKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVRVGKVLCSPVESEYISAEQIVCE  945
Sbjct:  1     PVITSISPSSGPLSGGTEITITGSNLGS---GEDIKVTFGGTECDVVSQEA---SQIVCK  54

Query:  946   IGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFV  981
Sbjct:  55    TPPYANGGPQPVTVSLDGGGLSS-----SPVTFTYV  85
```

Table 12I. Domain Analysis of NOV12

gnl|Pfam|pfam01833, TIG, IPT/TIG domain. This family consists of a domain that has an immunoglobulin like fold. These domains are found in cell surface receptors such as Met and Ron as well as in intracellular transcription factors where it is involved in DNA binding. (SEQ ID NO:115)
CD-Length = 85 residues, 100.0% aligned
Score = 46.6 bits (109), Expect = 1e-05

```
Query:  1173  PVLEPLSPTGLLELKPSSPLILKGRNLLPPAPGNSRLNYTVLIGSTPCTLT-VSETQLLC  1231
Sbjct:  1     PVITSISPSSG-PLSGGTEITITGSNL------GSGEDIKVTFGGTECDVVSQEASQIVC  53

Query:  1232  EAPNLTGQH----KVTVRAGGFEFSPGTLQVY  1259
Sbjct:  54    KTPPYANGGPQPVTVSLDGGGLSSSPVTFTYV  85
```

Table 12J. Domain Analysis of NOV12

gnl|Smart|smart00429, IPT, ig-like, plexins, transcription factors (SEQ ID NO:116)
CD-Length = 93 residues, 100.0% aligned
Score = 70.9 bits (172), Expect = 6e-13

```
Query:  885   DPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVRVGKVLCSPVESEYISAEQIVC  944
Sbjct:  1     DPVITRISPNSGPLSGGTRITLCGKNLDS-ISVVFVEVGVGEVPCTFLPSDV-SQTAIVC  58
```

```
Query:  945   EIGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFV  981
              +              | | |   +       |  ||+|
Sbjct:  59    KTP-PYHNIPGSVPVRVEVGLRNGGVPG-EPSPFTYV  93
```

Table 12K. Domain Analysis of NOV12

gnl|Pfam|pfam01437, Plexin_repeat, Plexin repeat. A cysteine rich repeat found in several different extracellular receptors. The function of the repeat is unknown. Three copies of the repeat are found Plexin. Two copies of the repeat are found in mahogany protein. A related C. elegans protein contains four copies of the repeat. The Met receptor contains a single copy of the repeat. The Pfam alignment shows 6 conserved cysteine residues that may form three conserved disulphide bridges. (SEQ ID NO:117)
CD-Length = 48 residues, 100.0% aligned
Score = 59.3 bits (142), Expect = 2e-09

```
Query:  532   SCVQYTSCELCLGSRDPHCGWCVLHSMCSRRDACERADEPQRFAADLLQCV  582
              +| |+|||  || + || ||||     |+| + | |    + ++     |
Sbjct:  1     NCSQHTSCGSCLSAPDPGCGWCPSRKRCTRLEECSR---GEGWSQSQETCP  48
```

Table 12L. Domain Analysis of NOV12

gnl|Pfam|pfam01437, Plexin_repeat, Plexin repeat. A cysteine rich repeat found in several different extracellular receptors. The function of the repeat is unknown. Three copies of the repeat are found Plexin. Two copies of the repeat are found in mahogany protein. A related C. elegans protein contains four copies of the repeat. The Met receptor contains a single copy of the repeat. The Pfam alignment shows 6 conserved cysteine residues that may form three conserved disulphide bridges. (SEQ ID NO:117)
CD-Length = 48 residues, 100.0% aligned
Score = 53.5 bits (127), Expect = 1e-07

```
Query:  681   NCSVHQSSCLSCVNGSFP-CHWCKYRHVCTHNVADCAFLEGRVNVSEDCP  729
              ||| | | | ||++   | | ||  |  ||    +|+  ||     | ||
Sbjct:  1     NCSQHTS-CGSCLSAPDPGCGWCPSRKRCTRL-EECSRGEGWSQSQETCP  48
```

Table 12M. Domain Analysis of NOV12

gnl|Pfam|pfam01437, Plexin_repeat, Plexin repeat. A cysteine rich repeat found in several different extracellular receptors. The function of the repeat is unknown. Three copies of the repeat are found Plexin. Two copies of the repeat are found in mahogany protein. A related C. elegans protein contains four copies of the repeat. The Met receptor contains a single copy of the repeat. The Pfam alignment shows 6 conserved cysteine residues that may form three conserved disulphide bridges. (SEQ ID NO:117)
CD-Length = 48 residues, 89.6% aligned
Score = 46.2 bits (108), Expect = 2e-05

```
Query:  835   RESCGLCLKADPRFECGWCVAERRCSLRHHCAADTPASWMHARHGSSRC  883
              |||  ||  |  |    |||| + +||+     |      +          |
Sbjct:  5     HTSCGSCLSA-PDPGCGWCPSRKRCTRLEEC-----SRGEGWSQSQETC  47
```

Table 12N. Domain Analysis of NOV12

gnl|Smart|smart00423, PSI, domain found in Plexins, Semaphorins and Integrins (SEQ ID NO:118)
CD-Length = 47 residues, 89.4% aligned
Score = 44.3 bits (103), Expect = 6e-05

```
Query:  833   ALRESCGLCLKADPRFECGWCVAERRCSLRHHCAADTPASWMHA  876
              +   ||  ||  |   + |  ||  ++  ||+     | +     +|
Sbjct:  3     SAYTSCSECLLARDPY-CAWCSSQGRCTSGERCDS-LRQNWSSG  44
```

Plexin is a type I membrane protein which was identified in Xenopus nervous system by hybridoma technique. Molecular cloning studies demonstrated that the extracellular segment of the plexin protein possesses three internal repeats of cysteine cluster which are homologous to the cysteine-rich domain of the c-met proto-oncogene protein product. A cell aggregation test revealed that the plexin protein mediated cell adhesion via a homophilic binding mechanism, in the presence of calcium ions. Plexin was expressed in the neuronal elements composing particular neuron circuits in Xenopus CNS and PNS. These findings indicate that plexin is a new member of the Ca(2+)-dependent cell adhesion molecules, and suggest that the molecule plays an important role in neuronal cell contact and neuron network formation.

In the developing nervous system axons navigate with great precision over large distances to reach their target areas. Chemorepulsive signals such as the semaphorins play an essential role in this process. The effects of one of these repulsive cues, semaphorin 3A (Sema3A), are mediated by the membrane protein neuropilin-1 (Npn-1). Recent work has shown that neuropilin-1 is essential but not sufficient to form functional Sema3A receptors and indicates that additional components are required to transduce signals from the cell surface to the cytoskeleton. Members of the plexin family interact with the neuropilins and act as co-receptors for Sema3A. Neuropilin/plexin interaction restricts the binding specificity of neuropilin-1 and allows the receptor complex to discriminate between two different semaphorins. Deletion of the highly conserved cytoplasmic domain of Plexin-A1 or -A2 creates a dominant negative Sema3A receptor that renders sensory axons resistant to the repulsive effects of Sema3A when expressed in sensory ganglia. These data suggest that functional semaphorin receptors contain plexins as signal-transducing and neuropilins as ligand-binding subunits.

Physiologic SEMA3A receptors consist of NRP1/PLXN1 complexes. Two semaphorin-binding proteins, plexin-1 (PLXN1) and neuropilin-1 (NRP1; 602069), form a stable complex. While SEMA3A binding to NRP1 does not alter nonneuronal cell morphology, SEMA3A interaction with NRP1/PLXN1 complexes induces adherent cells to round up. Expression of a dominant-negative PLXN1 in sensory neurons blocked SEMA3A-induced growth cone collapse. SEMA3A treatment led to the redistribution of growth cone NRP1 and PLXN1 into clusters.

The semaphorin family of proteins constitute one of the major cues for axonal guidance. The prototypic member of this family is Sema3A, previously designated semD/III or collapsin-1. Sema3A acts as a diffusible, repulsive guidance cue in vivo for the peripheral projections of embryonic dorsal root ganglion neurons. Sema3A binds with high affinity to neuropilin-1 on growth cone filopodial tips. Although neuropilin-1 is required for Sema3A action, it is incapable of transmitting a Sema3A signal to the growth cone interior. Instead, the Sema3A/neuropilin-1 complex interacts with another transmembrane protein, plexin, on the surface of growth cones. Certain semaphorins, other than Sema3A, can bind directly to plexins. The intracellular domain of plexin is responsible for initiating the signal transduction cascade leading to growth cone collapse, axon repulsion, or growth cone turning. This intracellular cascade involves the monomeric G-protein, Rac1, and a family of neuronal proteins, the CRMPs. Rac1 is likely to be involved in semaphorin-induced rearrangements of the actin cytoskeleton, but how plexin controls Rac1 activity is not known. Vertebrate CRMPs are homologous to the Caenorhabditis elegans unc-33 protein, which is required for proper axon morphology in worms. CRMPs are essential for Sema3A-induced, neuropilin-plexin-mediated growth cone collapse, but the molecular interactions of growth cone CRMPs are not well defined. Mechanistic aspects of plexin-based signaling for semaphorin guidance cues may have implications for other axon guidance events and for the basis of growth cone motility.

In Drosophila, plexin A is a functional receptor for semaphorin-1a. The human plexin gene family comprises at least nine members in four subfamilies. Plexin-B1 is a receptor for the transmembrane semaphorin Sema4D (CD100), and plexin-C1 is a receptor for the GPI-anchored semaphorin Sema7A (Sema-K1). Secreted (class 3) semaphorins do not bind directly to plexins, but rather plexins associate with neuropilins, coreceptors for these semaphorins. Plexins are widely expressed: in neurons, the expression of a truncated plexin-A1 protein blocks axon repulsion by Sema3A. The cytoplasmic domain of plexins associates with a tyrosine kinase activity. Plexins may also act as ligands mediating repulsion in epithelial cells

in vitro. Thus, plexins are receptors for multiple (and perhaps all) classes of semaphorins, either alone or in combination with neuropilins, and trigger a novel signal transduction pathway controlling cell repulsion.

In addition, recent studies have identified semaphorins and their receptors as putative molecular cues involved in olfactory pathfinding, plasticity and regeneration. The semaphorins comprise a large family of secreted and transmembrane axon guidance proteins, being either repulsive or attractive in nature. Neuropilins were shown to serve as receptors for secreted class 3 semaphorins, whereas members of the plexin family are receptors for class 1 and V (viral) semaphorins.

The disclosed NOV12 nucleic acid of the invention encoding a Plexin-1-like protein includes the nucleic acid whose sequence is provided in Table 12A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 12A while still encoding a protein that maintains its Plexin-1-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 29 percent of the bases may be so changed.

The disclosed NOV12 protein of the invention includes the Plexin-1-like protein whose sequence is provided in Table 12B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 12B, while still encoding a protein that maintains its Plexin-1-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 29 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the plexin-1-like protein and the NOV12 protein disclosed herein suggest that this plexin-1-like protein may have important structural and/or physiological functions characteristic of the mannosidase

protein family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These applications include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

The NOV12 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from AIDS, cancer therapy, treatment of Neurologic diseases, Brain and/or autoimmune disorders like encephalomyelitis, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, endocrine diseases, muscle disorders, inflammation and wound repair, bacterial, fungal, protozoal and viral infections (particularly infections caused by HIV-1 or HIV-2), pain, cancer (including but not limited to Neoplasm; adenocarcinoma; lymphoma; prostate cancer; uterus cancer), anorexia, bulimia, asthma, Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, Crohn's disease; multiple sclerosis; and Treatment of Albright Hereditary Ostoeodystrophy, angina pectoris, myocardial infarction, ulcers, asthma, allergies, benign prostatic hypertrophy, and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette syndrome, and/or other pathologies/disorders. The NOV12 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV12 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV12 protein have multiple hydrophilic regions, each of which can be used as an immunogen. This novel protein also has value in development of powerful assay system for functional analysis of various human

disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOVX Nucleic Acids and Polypeptides

One aspect of the invention pertains to isolated nucleic acid molecules that encode NOVX polypeptides or biologically active portions thereof. Also included in the invention are nucleic acid fragments sufficient for use as hybridization probes to identify NOVX-encoding nucleic acids (*e.g.*, NOVX mRNAs) and fragments for use as PCR primers for the amplification and/or mutation of NOVX nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule may be single-stranded or double-stranded, but preferably is comprised double-stranded DNA.

An NOVX nucleic acid can encode a mature NOVX polypeptide. As used herein, a "mature" form of a polypeptide or protein disclosed in the present invention is the product of a naturally occurring polypeptide or precursor form or proprotein. The naturally occurring polypeptide, precursor or proprotein includes, by way of nonlimiting example, the full-length gene product, encoded by the corresponding gene. Alternatively, it may be defined as the polypeptide, precursor or proprotein encoded by an ORF described herein. The product "mature" form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps as they may take place within the cell, or host cell, in which the gene product arises. Examples of such processing steps leading to a "mature" form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an ORF, or the proteolytic cleavage of a signal peptide or leader sequence. Thus a mature form arising from a precursor polypeptide or protein that has residues 1 to N, where residue 1 is the N-terminal methionine, would have residues 2 through N remaining after removal of the N-terminal methionine. Alternatively, a mature form arising from a precursor polypeptide or protein having residues 1 to N, in which an N-terminal signal sequence from residue 1 to residue M is cleaved, would have the residues from residue M+1 to residue N remaining. Further as used herein, a "mature" form of a polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation,

myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

The term "probes", as utilized herein, refers to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as approximately, *e.g.*, 6,000 nt, depending upon the specific use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are generally obtained from a natural or recombinant source, are highly specific, and much slower to hybridize than shorter-length oligomer probes. Probes may be single- or double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

The term "isolated" nucleic acid molecule, as utilized herein, is one, which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5'- and 3'-termini of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated NOVX nucleic acid molecules can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell/tissue from which the nucleic acid is derived (*e.g.*, brain, heart, liver, spleen, etc.). Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, or a complement of this aforementioned nucleotide sequence, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31 as a hybridization probe, NOVX molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, *et al.*, (eds.), MOLECULAR CLONING: A LABORATORY MANUAL 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard

PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to NOVX nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues, which oligonucleotide has a sufficient number of nucleotide bases to be used in a PCR reaction. A short oligonucleotide sequence may be based on, or designed from, a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a nucleic acid sequence having about 10 nt, 50 nt, or 100 nt in length, preferably about 15 nt to 30 nt in length. In one embodiment of the invention, an oligonucleotide comprising a nucleic acid molecule less than 100 nt in length would further comprise at least 6 contiguous nucleotides SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, or a complement thereof. Oligonucleotides may be chemically synthesized and may also be used as probes.

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, or a portion of this nucleotide sequence (*e.g.*, a fragment that can be used as a probe or primer or a fragment encoding a biologically-active portion of an NOVX polypeptide). A nucleic acid molecule that is complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 31 is one that is sufficiently complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 31 that it can hydrogen bond with little or no mismatches to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, thereby forming a stable duplex.

As used herein, the term "complementary" refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term "binding" means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, van der Waals, hydrophobic interactions, and the like. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the

effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively, and are at most some portion less than a full length sequence. Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences or amino acid sequences formed from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences or amino acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in respect to certain components or side chains. Analogs may be synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type. Homologs are nucleic acid sequences or amino acid sequences of a particular gene that are derived from different species.

Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below. Derivatives or analogs of the nucleic acids or proteins of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids or proteins of the invention, in various embodiments, by at least about 70%, 80%, or 95% identity (with a preferred identity of 80-95%) over a nucleic acid or amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. *See e.g.* Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below.

A "homologous nucleic acid sequence" or "homologous amino acid sequence," or variations thereof, refer to sequences characterized by a homology at the nucleotide level or amino acid level as discussed above. Homologous nucleotide sequences encode those sequences coding for isoforms of NOVX polypeptides. Isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. In the invention, homologous nucleotide sequences include nucleotide sequences encoding for an NOVX polypeptide of species other than humans, including, but not limited to: vertebrates, and thus can include, *e.g.*, frog, mouse, rat, rabbit, dog, cat cow, horse, and other organisms. Homologous nucleotide

sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the exact nucleotide sequence encoding human NOVX protein. Homologous nucleic acid sequences include those nucleic acid sequences that encode conservative amino acid substitutions (see below) in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, as well as a polypeptide possessing NOVX biological activity. Various biological activities of the NOVX proteins are described below.

An NOVX polypeptide is encoded by the open reading frame ("ORF") of an NOVX nucleic acid. An ORF corresponds to a nucleotide sequence that could potentially be translated into a polypeptide. A stretch of nucleic acids comprising an ORF is uninterrupted by a stop codon. An ORF that represents the coding sequence for a full protein begins with an ATG "start" codon and terminates with one of the three "stop" codons, namely, TAA, TAG, or TGA. For the purposes of this invention, an ORF may be any part of a coding sequence, with or without a start codon, a stop codon, or both. For an ORF to be considered as a good candidate for coding for a *bona fide* cellular protein, a minimum size requirement is often set, *e.g.*, a stretch of DNA that would encode a protein of 50 amino acids or more.

The nucleotide sequences determined from the cloning of the human NOVX genes allows for the generation of probes and primers designed for use in identifying and/or cloning NOVX homologues in other cell types, *e.g.* from other tissues, as well as NOVX homologues from other vertebrates. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, 50, 100, 150, 200, 250, 300, 350 or 400 consecutive sense strand nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 31; or an anti-sense strand nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 31; or of a naturally occurring mutant of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31.

Probes based on the human NOVX nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In various embodiments, the probe further comprises a label group attached thereto, *e.g.* the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissues which mis-express an NOVX protein, such as by measuring a level of an NOVX-encoding nucleic acid in a sample of cells from a subject *e.g.*, detecting NOVX mRNA levels or determining whether a genomic NOVX gene has been mutated or deleted.

"A polypeptide having a biologically-active portion of an NOVX polypeptide" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. A nucleic acid fragment encoding a "biologically-active portion of NOVX" can be prepared by isolating a portion SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, or 31, that encodes a polypeptide having an NOVX biological activity (the biological activities of the NOVX proteins are described below), expressing the encoded portion of NOVX protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of NOVX.

NOVX Nucleic Acid and Polypeptide Variants

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31 due to degeneracy of the genetic code and thus encode the same NOVX proteins as that encoded by the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32.

In addition to the human NOVX nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the NOVX polypeptides may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the NOVX genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame (ORF) encoding an NOVX protein, preferably a vertebrate NOVX protein. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of the NOVX genes. Any and all such nucleotide variations and resulting amino acid polymorphisms in the NOVX polypeptides, which are the result of natural allelic variation and that do not alter the functional activity of the NOVX polypeptides, are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding NOVX proteins from other species, and thus that have a nucleotide sequence that differs from the human SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31 are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of

the NOVX cDNAs of the invention can be isolated based on their homology to the human NOVX nucleic acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 6 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31. In another embodiment, the nucleic acid is at least 10, 25, 50, 100, 250, 500, 750, 1000, 1500, or 2000 or more nucleotides in length. In yet another embodiment, an isolated nucleic acid molecule of the invention hybridizes to the coding region. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other.

Homologs (*i.e.*, nucleic acids encoding NOVX proteins derived from species other than human) or other related sequences (*e.g.*, paralogs) can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular human sequence as a probe using methods well known in the art for nucleic acid hybridization and cloning.

As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences. Generally, stringent conditions are selected to be about 5 °C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at Tm, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (*e.g.*, 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other. A non-limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C. An isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In a second embodiment, a nucleic acid sequence that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, or fragments, analogs or derivatives thereof, under conditions of moderate stringency is provided. A non-limiting example of moderate stringency hybridization conditions are hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS at 37°C. Other conditions of moderate stringency that may be used are well-known within the art. *See, e.g.*, Ausubel, et *al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990; GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

In a third embodiment, a nucleic acid that is hybridizable to the nucleic acid molecule comprising the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, or fragments, analogs or derivatives thereof, under conditions of low stringency, is provided. A non-limiting example of low stringency hybridization conditions are hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40°C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50°C. Other conditions of low stringency that may be used are well known in the art (*e.g.*, as employed for cross-species hybridizations). *See, e.g.*, Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY

MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981. *Proc Natl Acad Sci USA* **78**: 6789-6792.

Conservative Mutations

In addition to naturally-occurring allelic variants of NOVX sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, thereby leading to changes in the amino acid sequences of the encoded NOVX proteins, without altering the functional ability of said NOVX proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequences of the NOVX proteins without altering their biological activity, whereas an "essential" amino acid residue is required for such biological activity. For example, amino acid residues that are conserved among the NOVX proteins of the invention are predicted to be particularly non-amenable to alteration. Amino acids for which conservative substitutions can be made are well-known within the art.

Another aspect of the invention pertains to nucleic acid molecules encoding NOVX proteins that contain changes in amino acid residues that are not essential for activity. Such NOVX proteins differ in amino acid sequence from SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 45% homologous to the amino acid sequences SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32. Preferably, the protein encoded by the nucleic acid molecule is at least about 60% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, and 32; more preferably at least about 70% homologous SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32; still more preferably at least about 80% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32; even more preferably at least about 90% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32; and most preferably at least about 95% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32.

An isolated nucleic acid molecule encoding an NOVX protein homologous to the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32 can be

created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein.

Mutations can be introduced into SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted, non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined within the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted non-essential amino acid residue in the NOVX protein is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an NOVX coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for NOVX biological activity to identify mutants that retain activity. Following mutagenesis SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, the encoded protein can be expressed by any recombinant technology known in the art and the activity of the protein can be determined.

The relatedness of amino acid families may also be determined based on side chain interactions. Substituted amino acids may be fully conserved "strong" residues or fully conserved "weak" residues. The "strong" group of conserved amino acid residues may be any one of the following groups: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW, wherein the single letter amino acid codes are grouped by those amino acids that may be substituted for each other. Likewise, the "weak" group of conserved residues may be any one of the following: CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, VLIM, HFY, wherein the letters within each group represent the single letter amino acid code.

In one embodiment, a mutant NOVX protein can be assayed for (*i*) the ability to form protein:protein interactions with other NOVX proteins, other cell-surface proteins, or biologically-active portions thereof, (*ii*) complex formation between a mutant NOVX protein

and an NOVX ligand; or (*iii*) the ability of a mutant NOVX protein to bind to an intracellular target protein or biologically-active portion thereof; (*e.g.* avidin proteins).

In yet another embodiment, a mutant NOVX protein can be assayed for the ability to regulate a specific biological function (*e.g.*, regulation of insulin release).

Antisense Nucleic Acids

Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein (*e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence). In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire NOVX coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of an NOVX protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32, or antisense nucleic acids complementary to an NOVX nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31, are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding an NOVX protein. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence encoding the NOVX protein. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

Given the coding strand sequences encoding the NOVX protein disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of NOVX mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of NOVX mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of NOVX mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15,

20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally-occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids (*e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used).

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an NOVX protein to thereby inhibit expression of the protein (*e.g.*, by inhibiting transcription and/or translation). The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface

(*e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens). The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient nucleic acid molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other. *See, e.g.,* Gaultier, *et al.*, 1987. *Nucl. Acids Res.* **15**: 6625-6641. The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (*See, e.g.,* Inoue, *et al.* 1987. *Nucl. Acids Res.* **15**: 6131-6148) or a chimeric RNA-DNA analogue (*See, e.g.,* Inoue, *et al.*, 1987. *FEBS Lett.* **215**: 327-330.

Ribozymes and PNA Moieties

Nucleic acid modifications include, by way of non-limiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.

In one embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach 1988. *Nature* 334: 585-591) can be used to catalytically cleave NOVX mRNA transcripts to thereby inhibit translation of NOVX mRNA. A ribozyme having specificity for an NOVX-encoding nucleic acid can be designed based upon the nucleotide sequence of an NOVX cDNA disclosed herein (*i.e.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an NOVX-encoding mRNA. *See, e.g.*, U.S. Patent 4,987,071 to Cech, *et al.* and U.S. Patent 5,116,742 to Cech, *et al.* NOVX mRNA can also be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. *See, e.g.*, Bartel *et al.*, (1993) *Science* 261:1411-1418.

Alternatively, NOVX gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the NOVX nucleic acid (*e.g.*, the NOVX promoter and/or enhancers) to form triple helical structures that prevent transcription of the NOVX gene in target cells. *See, e.g.*, Helene, 1991. *Anticancer Drug Des.* 6: 569-84; Helene, *et al.* 1992. *Ann. N.Y. Acad. Sci.* 660: 27-36; Maher, 1992. *Bioassays* 14: 807-15.

In various embodiments, the NOVX nucleic acids can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids. *See, e.g.*, Hyrup, *et al.*, 1996. *Bioorg Med Chem* 4: 5-23. As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics (*e.g.*, DNA mimics) in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup, *et al.*, 1996. *supra*; Perry-O'Keefe, *et al.*, 1996. *Proc. Natl. Acad. Sci. USA* 93: 14670-14675.

PNAs of NOVX can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs of NOVX can also be used, for example, in the analysis of single base pair mutations in a gene (*e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S_1 nucleases (*See,* Hyrup, *et al.*, 1996.*supra*); or as probes or primers for DNA sequence and hybridization (*See,* Hyrup, *et al.*, 1996, *supra*; Perry-O'Keefe, *et al.*, 1996. *supra*).

In another embodiment, PNAs of NOVX can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of NOVX can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes (*e.g.*, RNase H and DNA polymerases) to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (*see,* Hyrup, et al., *1996. supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup, *et al.*, 1996.

supra and Finn, *et al.*, 1996. *Nucl Acids Res* 24: 3357-3363. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, *e.g.*, 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA. *See, e.g.*, Mag, *et al.*, 1989. *Nucl Acid Res* 17: 5973-5988. PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment. *See, e.g.*, Finn, *et al.*, 1996. *supra*. Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. *See, e.g.*, Petersen, *et al.*, 1975. *Bioorg. Med. Chem. Lett.* 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (*see, e.g.*, Letsinger, *et al.*, 1989. *Proc. Natl. Acad. Sci. U.S.A.* 86: 6553-6556; Lemaitre, *et al.*, 1987. *Proc. Natl. Acad. Sci.* 84: 648-652; PCT Publication No. WO88/09810) or the blood-brain barrier (*see, e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (*see, e.g.*, Krol, *et al.*, 1988. *BioTechniques* 6:958-976) or intercalating agents (*see, e.g.*, Zon, 1988. *Pharm. Res.* 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, and the like.

NOVX Polypeptides

A polypeptide according to the invention includes a polypeptide including the amino acid sequence of NOVX polypeptides whose sequences are provided in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residues shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32 while still encoding a protein that maintains its NOVX activities and physiological functions, or a functional fragment thereof.

In general, an NOVX variant that preserves NOVX-like function includes any variant in which residues at a particular position in the sequence have been substituted by other amino acids, and further include the possibility of inserting an additional residue or residues between two residues of the parent protein as well as the possibility of deleting one or more residues from the parent sequence. Any amino acid substitution, insertion, or deletion is encompassed

by the invention. In favorable circumstances, the substitution is a conservative substitution as defined above.

One aspect of the invention pertains to isolated NOVX proteins, and biologically-active portions thereof, or derivatives, fragments, analogs or homologs thereof. Also provided are polypeptide fragments suitable for use as immunogens to raise anti-NOVX antibodies. In one embodiment, native NOVX proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, NOVX proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, an NOVX protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the NOVX protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of NOVX proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the language "substantially free of cellular material" includes preparations of NOVX proteins having less than about 30% (by dry weight) of non-NOVX proteins (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-NOVX proteins, still more preferably less than about 10% of non-NOVX proteins, and most preferably less than about 5% of non-NOVX proteins. When the NOVX protein or biologically-active portion thereof is recombinantly-produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the NOVX protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins having less than about 30% (by dry weight) of chemical precursors or non-NOVX chemicals, more preferably less than about 20% chemical precursors or non-NOVX chemicals, still more preferably less than about 10% chemical precursors or non-NOVX chemicals, and most preferably less than about 5% chemical precursors or non-NOVX chemicals.

Biologically-active portions of NOVX proteins include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequences of the NOVX proteins (*e.g.*, the amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32) that include fewer amino acids than the full-length NOVX proteins, and exhibit at least one activity of an NOVX protein. Typically, biologically-active portions comprise a domain or motif with at least one activity of the NOVX protein. A biologically-active portion of an NOVX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acid residues in length.

Moreover, other biologically-active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native NOVX protein.

In an embodiment, the NOVX protein has an amino acid sequence shown SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32. In other embodiments, the NOVX protein is substantially homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32, and retains the functional activity of the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail, below. Accordingly, in another embodiment, the NOVX protein is a protein that comprises an amino acid sequence at least about 45% homologous to the amino acid sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32, and retains the functional activity of the NOVX proteins of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32.

Determining Homology Between Two or More Sequences

To determine the percent homology of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are homologous at that position (*i.e.*, as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity").

The nucleic acid sequence homology may be determined as the degree of identity between two sequences. The homology may be determined using computer programs known

in the art, such as GAP software provided in the GCG program package. *See,* Needleman and Wunsch, 1970. *J Mol Biol* 48: 443-453. Using GCG GAP software with the following settings for nucleic acid sequence comparison: GAP creation penalty of 5.0 and GAP extension penalty of 0.3, the coding region of the analogous nucleic acid sequences referred to above exhibits a degree of identity preferably of at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, with the CDS (encoding) part of the DNA sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 31.

The term "sequence identity" refers to the degree to which two polynucleotide or polypeptide sequences are identical on a residue-by-residue basis over a particular region of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, U, or I, in the case of nucleic acids) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 80 percent sequence identity, preferably at least 85 percent identity and often 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison region.

Chimeric and Fusion Proteins

The invention also provides NOVX chimeric or fusion proteins. As used herein, an NOVX "chimeric protein" or "fusion protein" comprises an NOVX polypeptide operatively-linked to a non-NOVX polypeptide. An "NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to an NOVX protein SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, or 32, whereas a "non-NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the NOVX protein, *e.g.*, a protein that is different from the NOVX protein and that is derived from the same or a different organism. Within an NOVX fusion protein the NOVX polypeptide can correspond to all or a portion of an NOVX protein. In one embodiment, an NOVX fusion protein comprises at least one biologically-active portion of an NOVX protein. In another embodiment, an NOVX fusion protein comprises at least two biologically-active portions of an NOVX protein. In yet another embodiment, an NOVX

fusion protein comprises at least three biologically-active portions of an NOVX protein. Within the fusion protein, the term "operatively-linked" is intended to indicate that the NOVX polypeptide and the non-NOVX polypeptide are fused in-frame with one another. The non-NOVX polypeptide can be fused to the N-terminus or C-terminus of the NOVX polypeptide.

In one embodiment, the fusion protein is a GST-NOVX fusion protein in which the NOVX sequences are fused to the C-terminus of the GST (glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant NOVX polypeptides.

In another embodiment, the fusion protein is an NOVX protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of NOVX can be increased through use of a heterologous signal sequence.

In yet another embodiment, the fusion protein is an NOVX-immunoglobulin fusion protein in which the NOVX sequences are fused to sequences derived from a member of the immunoglobulin protein family. The NOVX-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between an NOVX ligand and an NOVX protein on the surface of a cell, to thereby suppress NOVX-mediated signal transduction *in vivo*. The NOVX-immunoglobulin fusion proteins can be used to affect the bioavailability of an NOVX cognate ligand. Inhibition of the NOVX ligand/NOVX interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, as well as modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the NOVX-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-NOVX antibodies in a subject, to purify NOVX ligands, and in screening assays to identify molecules that inhibit the interaction of NOVX with an NOVX ligand.

An NOVX chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be

carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.,* Ausubel, *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). An NOVX-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the NOVX protein.

NOVX Agonists and Antagonists

The invention also pertains to variants of the NOVX proteins that function as either NOVX agonists (*i.e.,* mimetics) or as NOVX antagonists. Variants of the NOVX protein can be generated by mutagenesis (*e.g.*, discrete point mutation or truncation of the NOVX protein). An agonist of the NOVX protein can retain substantially the same, or a subset of, the biological activities of the naturally occurring form of the NOVX protein. An antagonist of the NOVX protein can inhibit one or more of the activities of the naturally occurring form of the NOVX protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the NOVX protein. Thus, specific biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the NOVX proteins.

Variants of the NOVX proteins that function as either NOVX agonists (*i.e.,* mimetics) or as NOVX antagonists can be identified by screening combinatorial libraries of mutants (*e.g.*, truncation mutants) of the NOVX proteins for NOVX protein agonist or antagonist activity. In one embodiment, a variegated library of NOVX variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of NOVX variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential NOVX sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of NOVX sequences therein. There are a variety of methods which can be used to produce libraries of potential NOVX variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate

set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential NOVX sequences. Methods for synthesizing degenerate oligonucleotides are well-known within the art. *See, e.g.,* Narang, 1983. *Tetrahedron* 39: 3; Itakura, *et al.*, 1984. *Annu. Rev. Biochem.* 53: 323; Itakura, *et al.*, 1984. *Science* 198: 1056; Ike, *et al.*, 1983. *Nucl. Acids Res.* 11: 477.

Polypeptide Libraries

In addition, libraries of fragments of the NOVX protein coding sequences can be used to generate a variegated population of NOVX fragments for screening and subsequent selection of variants of an NOVX protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an NOVX coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S_1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, expression libraries can be derived which encodes N-terminal and internal fragments of various sizes of the NOVX proteins.

Various techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of NOVX proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique that enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify NOVX variants. *See, e.g.,* Arkin and Yourvan, 1992. *Proc. Natl. Acad. Sci. USA* 89: 7811-7815; Delgrave, *et al.*, 1993. *Protein Engineering* 6:327-331.

Anti-NOVX Antibodies

Also included in the invention are antibodies to NOVX proteins, or fragments of NOVX proteins. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab}, $F_{ab'}$ and $F_{(ab')2}$ fragments, and an F_{ab} expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG_1, IgG_2, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated NOVX-related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of NOVX-related protein that is located on the surface of the protein, *e.g.*, a hydrophilic region. A hydrophobicity analysis of the human NOVX-related protein sequence will indicate which regions of a NOVX-related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, *e.g.*, Hopp and Woods, 1981, *Proc. Nat. Acad. Sci. USA* 78:

3824-3828; Kyte and Doolittle 1982, *J. Mol. Biol.* 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, Antibodies: A Laboratory Manual, Harlow and Lane, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

Polyclonal Antibodies

For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific

antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

Monoclonal Antibodies

The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., MONOCLONAL ANTIBODY PRODUCTION TECHNIQUES AND APPLICATIONS, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980).. Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to

obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *Nature* 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

Humanized Antibodies

The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeyen et al., *Science*, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)).

Human Antibodies

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (*Bio/Technology* 10, 779-783 (1992)); Lonberg et al. (*Nature* 368 856-859 (1994)); Morrison (*Nature* 368, 812-13 (1994)); Fishwild et al,(*Nature Biotechnology* 14, 845-51 (1996)); Neuberger (*Nature Biotechnology* 14, 826 (1996)); and Lonberg and Huszar (*Intern. Rev. Immunol.* 13 65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full

complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the Xenomouse™ as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

F_{ab} Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of F_{ab} expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective

identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an $F_{(ab')2}$ fragment produced by pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated by reducing the disulfide bridges of an $F_{(ab')2}$ fragment; (iii) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., *Methods in Enzymology*, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part

of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. $F(ab')_2$ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol com26S protease regulatory subunit 4g agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175:217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has

provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., *J. Immunol.* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

Effector Function Engineering

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates

(such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

In one embodiment, methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) and other immunologically-mediated techniques known within the art. In a specific embodiment, selection of antibodies that are specific to a particular domain of an NOVX protein is facilitated by generation of hybridomas that bind to the fragment of an NOVX protein possessing such a domain. Thus, antibodies that are specific for a desired domain within an NOVX protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

Anti-NOVX antibodies may be used in methods known within the art relating to the localization and/or quantitation of an NOVX protein (*e.g.*, for use in measuring levels of the NOVX protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies for NOVX proteins, or derivatives, fragments, analogs or homologs thereof, that contain the antibody derived binding domain, are utilized as pharmacologically-active compounds (hereinafter "Therapeutics").

An anti-NOVX antibody (*e.g.*, monoclonal antibody) can be used to isolate an NOVX polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-NOVX antibody can facilitate the purification of natural NOVX polypeptide from cells and of recombinantly-produced NOVX polypeptide expressed in host cells. Moreover, an anti-NOVX antibody can be used to detect NOVX protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the NOVX protein. Anti-NOVX antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the

antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

NOVX Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an NOVX protein, or derivatives, fragments, analogs or homologs thereof. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid

sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell).

The term "regulatory sequence" is intended to includes promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, NOVX proteins, mutant forms of NOVX proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of NOVX proteins in prokaryotic or eukaryotic cells. For example, NOVX proteins can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (*i*) to increase expression of recombinant protein; (*ii*) to increase the solubility of the recombinant protein; and (*iii*) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition